NOT CIRCULATE

UNIVERSITY OF MICHIGAN

JUL 8 - 1954

MEDICAL LIBRARY

VOLUME 94 NUMBER 6

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL

SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

June, 1954

Clinical Features of the Genetic Variants of Sickle Cell Disease. ERNEST W. SMITH AND C. LOCKARD CONLEY 289

Eosinophilia and Hepatomegaly Due to Capillaria Hepatica Infection. G. F. OTTO, M. BERTHRONG, R. E. APPLEBY, J. C. RAWLINS AND OSCAR WILBUR 319

The Evolution of Pulmonary Tuberculosis and Its Behavior Under Treatment. (Thayer Lecture II for 1953.) J. BURNS AMBERSON 337

Abstracts of Papers Presented Before The Johns Hopkins Medical Society in Association with the Alpha Omega Alpha Fraternity, April 12, 1954 348

Book Reviews 353

Index to Volume XCIV 357

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

COPYRIGHT, 1954, BY THE JOHNS HOPKINS PRESS

BULLETIN OF

THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, PHILIP F. WAGLEY

ASSOCIATE MANAGING EDITOR, VERNON B. MOUNTCASTLE

EDITORIAL BOARD

E. Cowles Andrus **Charles R. Austrian** **Henry T. Bahnson**
Kenneth C. Blanchard **John Eager Howard**
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Correspondence concerning business matters and all remittances should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

Subscription price. In the United States and its possessions $8.00 per year. In Canada $8.25 per year; in foreign countries $8.50 per year. Single numbers, $1.00.

New subscriptions and renewals are entered to begin with the first issue of the current year. Subscribers in the United States are hereby notified that missing numbers cannot be replaced unless notification of loss is received in this office within 1 month following publication of the missing number; foreign subscribers 6 months.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

Manuscripts. Manuscripts should be typewritten, one side of page only, and double-spaced. Following the title should appear the author's name, department, and the university and/or hospital he represents. A list of references (bibliography) in numerical sequence should appear at the end of article. Preferred style for references is as follows: Author's last name, initials. Title of book or article, with first word and proper names capitalized only. Name of journal (abbreviate), date of publication, volume number: page number. The Bulletin is not responsible for loss of a manuscript in mail. Author should retain a duplicate copy.

Illustrations and Tables. Legends are required for Figures and descriptive headings for Tables. Use Arabic numerals to number Figures (Fig. 1); use Roman numerals to number Plates and Tables (Plate I). It should be indicated exactly where Figures and Tables are to appear in text; Plates all appear at end of article. All Figures should be drafted in black India ink for 50% reduction to 4½ inch width. Glossy photographs must be supplied for all Plates. Original illustrations will be returned to author with galley proofs.

Reprints. Twenty-five reprints, without covers, are furnished gratis for each article. Additional reprints should be ordered when galley proofs are returned.

THE JOHNS HOPKINS PRESS

BALTIMORE-18, MARYLAND, U. S. A.

Entered as second class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918

CLINICAL FEATURES OF THE GENETIC VARIANTS OF SICKLE CELL DISEASE

ERNEST W. SMITH* AND C. LOCKARD CONLEY

Department of Medicine, The Johns Hopkins University School of Medicine and Hospital

Received for publication March 18, 1954

Individuals with the sickling phenomenon have been considered traditionally to have either sickle cell trait or sickle cell anemia. The sickle cell trait has been almost universally regarded as a completely benign inherited abnormality of the red cells, unassociated with anemia or other manifestations of disease. Sickle cell anemia, on the other hand, is a congenital, chronic, unrelenting disease associated with persistent hemolytic anemia, unremitting jaundice, and peculiar "crises" which lead to death in the majority of patients in childhood or early adult life. On clinical grounds the differentiation between sickle cell trait and sickle cell anemia is usually simple. Nevertheless, cases often have been encountered in which the differentiation was made difficult when anemia due to unrelated causes occurred in individuals with sicklemia. Furthermore, some patients have presented at times a pattern suggestive of the sickle cell trait, and at other times displayed manifestations characteristic of sickle cell anemia (1, 2, 3). Until recently no satisfactory explanation for these atypical cases was available.

In recent years several observations of fundamental importance have clarified our understanding of the factors which determine the clinical course of the individual with sicklemia. On the basis of family studies, Neel (4) concluded that the sickle cell trait occurs in persons who are heterozygous for the sickling character, while sickle cell anemia results from the inheritance of sickling genes from both parents. Suggestive evidence was obtained that the basic abnormality of the sickled erythrocyte lay within the hemoglobin (5, 6, 7). Impressive confirmation of this concept was provided by Pauling and his associates (8) who demonstrated that under appropriate conditions sickle cell hemoglobin has a characteristically different electrophoretic mobility than normal hemoglobin. These investigators further showed that the red cells of individuals with sickle cell trait contain a mixture of normal and sickle hemoglobin, while those of patients with sickle cell anemia contain only the abnormal hemoglobin. The use of the electrophoretic technique has made possible the differentiation between sickle cell trait and sickle cell anemia with certainty. In the study of certain atypical cases of sickle cell disease, Itano and Neel (9), and Itano (10)

This investigation was in part supported by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health.

* Clinical Fellow of the American Cancer Society.

discovered two previously unrecognized inherited abnormalities of hemoglobin. Each of these abnormal hemoglobins, when coexisting with sickle hemoglobin, gave rise to a disease which had been mistaken for sickle cell anemia. These newly discovered types of abnormal hemoglobin have been designated as *hemoglobin C* and *hemoglobin D* (11). Peculiarly, hemoglobin D has been reported in only one family to date. Hemoglobin C, however, is of common occurrence, appearing in the red cells of about 2 per cent of negroes examined (12). Hemoglobin C is readily differentiated electrophoretically from normal and sickle hemoglobin (9, 12, 13, 14, 15, 16, 17). It appears to be inherited as a simple Mendelian dominant character which is allelic with normal and sickle hemoglobins. Information concerning the clinical and hematologic manifestations of persons with hemoglobin C is rapidly accumulating (9, 12, 13, 14, 15). When an individual is heterozygous for both sickle and C hemoglobins, an extremely interesting disorder designated as *sickle cell-hemoglobin C disease* occurs, apparently the result of interaction of the two abnormal genes.

In addition to the inherited abnormalities of hemoglobin, other genetically determined abnormalities of the red cells are well known and include hereditary leptocytosis, hereditary spherocytosis and ovalocytosis. In rare instances, an individual may inherit a gene for sickling from one parent and a gene determining one of the other red cell abnormalities from the other parent. This has been reported to occur in a number of cases in which genes for sickling and leptocytosis (thalassemia) have been combined (18, 19, 20, 21, 22). The resultant disorder, sickle cell-thalassemia disease, presents features which indicate interaction between the abnormal genes.

The present report is concerned with the detailed clinical and hematologic study of 23 patients who were found to be heterozygous both for sickling and for one of the other inherited abnormalities of the red cells. The observations are compared with similar studies of 15 patients with classical sickle cell anemia.

METHODS

Terminology: Various types of hemoglobin have been designated in the manner recommended by a group of authorities in this field (11). Normal hemoglobin is designated as *A*, sickle hemoglobin, *S*, and the other abnormal hemoglobin encountered in this study, *C*. Hemoglobin resistant to alkali denaturation is *F* (fetal hemoglobin) and is not genetically determined.

The genetic make-up of the patients is indicated by letters and abbreviations as follows:

S-S sickle cell anemia
S-A sickle cell trait
S-C sickle cell-hemoglobin C disease
S-thal. sickle cell-thalassemia disease
S-CHJ sickle cell-congenital hemolytic jaundice

The term "sickle cell disease" is used broadly to include all of the disorders in which manifestations of disease seem attributable to the presence of S hemoglobin, whether the patient is homozygous or heterozygous for this abnormal hemoglobin. The abbreviations do not

imply that the hemoglobin in thalassemia or congenital hemolytic jaundice is abnormal. The term "crisis" is used to describe characteristic episodes of pain, fever and other features which occur in association with sicklemia, whether or not there is an associated increase in rate of blood destruction.

Hematologic data were obtained by use of the routine methods of our hematology laboratories. In addition a method of filter paper electrophoresis previously described for identifying normal, sickle, and C hemoglobins (12), and Singer's technique for determining alkali resistant hemoglobin fractions (23) were used.

CLINICAL MATERIAL

Fifteen individuals with sickle cell anemia (S-S group) were selected from a much larger number in our clinic files. Selection was not random but was made on the basis of completeness of clinical data over a period of years, with inclusion of certain individuals having clinical features of particular interest. In most respects, this restricted number of patients represents the classical pattern of sickle cell anemia and exceptions to this pattern will be specifically mentioned.

Sixteen patients with sickle cell-hemoglobin C disease (S-C group) have been studied in our clinic. Many of these were collected by re-evaluation of cases which had been considered "atypical" before the advent of knowledge concerning the genetic aspects of sickle cell disease. In addition to these 16 patients, we have included another negro female with sicklemia who had been considered atypical with respect to sickle cell anemia. Because of absence of anemia and of crises in childhood, she was first considered to have sickle cell trait, but subsequently developed severe hemolytic crises associated with marked enlargement of the spleen. In addition, there are many more than 50 per cent target cells on her blood smears. Because these findings are so similar to those seen in other patients with sickle cell-hemoglobin C disease, data concerning her clinical course are reported, although a diagnosis cannot be established since the patient is dead, and no members of her family are available for study.

Four patients with sickle cell-thalassemia disease (S-thal group) are presented. One patient is a negro and the other 3 are the only Caucasians in the entire series. Two of these patients were seen in the Johns Hopkins Hospital, one was seen in the Sinai Hospital in Baltimore through the courtesy of Dr. Stanley Miller and data on the fourth were provided by Dr. Barkley Beidleman*. Blood from all of these patients was available for study.

Two patients with unclassified sicklemia are included. These negro patients had a clinical course and a hematologic pattern which were quite distinct from sickle cell anemia. Electrophoretic studies showed that sickle and normal hemoglobins were present in percentages of approximately 80 and 15, with the remainder of the hemoglobin being alkali resistant and thus fetal in type. This electrophoretic pattern is suggestive of sickle cell-thalassemia disease, but diagnosis could not be established because other family members were not available for study. These patients are therefore considered unclassified.

One patient with sickle cell-congenital hemolytic jaundice (S-CHJ) was studied before and after splenectomy. This patient was hospitalized in the Baltimore City Hospitals and was examined by us through the courtesy of Dr. David Lukens and Dr. Julius Krevans who will report the case in detail (24).

---

* We are very grateful to Dr. Beidleman of Pensacola, Florida, and to Dr. Weems of Laural, Mississippi, who provided data including complete family study pertaining to this patient.

IDENTIFICATION OF THE PATIENT GROUPS

Filter paper electrophoresis of the hemoglobin was carried out on all of the patients included in this study with the exception of 4 who had died. All patients considered to have sickle cell anemia had hemoglobin which electrophoretically was virtually 100 per cent of the abnormal S variety. The small amounts of fetal hemoglobin present in these patients was not demonstrable by this method. In the sickle cell-hemoglobin C group, S and C hemoglobins were present in an approximate 50:50 ratio as estimated by visual comparison of the spots. In this group fetal hemoglobin was greater than 2 per cent in 5 of 9 cases tested, and was never greater than 6 per cent.

Electrophoretic studies were conducted on family members of 2 patients who had died. In one family the mother of the patient had the electrophoretic pattern of sickle cell trait and her red cells could be made to sickle. Of the patient's 2 children, one was found to have sickle cell trait and the other hemoglobin C trait. Since the premise that the patient had sickle cell anemia would demand that all of her children would have at least one sickling gene, it seems unreasonable to assume that she had other than sickle cell-hemoglobin C disease. The diagnosis of this disorder was established in the second patient in an identical fashion.

Three of the 4 patients considered to have sickle cell-thalassemia were white and 2 were of Greek extraction. The clinical and hematologic features of these patients were similar to those described in other cases (18, 19, 20, 21, 22). Family studies in 3 of the cases indicated that the patient had inherited a gene for sickling and one for thalassemia. Studies using electrophoretic and alkali denaturation techniques were done on 3 of the patients. Two patients had approximately 80 per cent S hemoglobin, 8 per cent fetal and the remainder normal. The third patient had 12 per cent fetal hemoglobin but the electrophoretic pattern could not be distinguished from that of sickle cell anemia. However, the patient's mother and 2 of his siblings were demonstrated to have red cells which could not be made to sickle and which contained no S hemoglobin on electrophoretic study. The blood smears of these same 3 individuals were characterized by hypochromia, stippling and target cells, a pattern which seems entirely compatible with thalassemia minor.

CLINICAL FEATURES OF THE VARIOUS SICKLE CELL DISEASES

General considerations: The clinical manifestations were more severe and life expectancy shorter in sickle cell anemia than in the variant forms of sicklemia. On clinical grounds alone patients with sickle cell anemia were easily distinguished from those with other forms of sickle cell disease. In our experience with a large number of patients with sickle cell anemia, there were only 2 exceptions to this generalization. These were brothers who had severe manifestations of sickle cell anemia for 18 and 20 years but then underwent remissions of anemia and crises for 4 or more years. Because of this atypical feature of their illness, they were at one time considered on clinical grounds to have one of the variant forms of sicklemia, but were proved to be homozygous for sickling. On the other hand, every patient found to have a genetic variant of sicklemia had been considered on clinical grounds alone to be atypical with respect to classical sickle cell anemia. When an individual who was heterozygous for sickling also inherited a gene for another red cell abnormality, the resultant disease was apparently determined by interaction of the 2 abnormal genes.

This was true of all of our cases with the possible exception of one who had sickle cell trait combined with hereditary spherocytosis. This case is to be described in detail by Lukens and Krevans (24) and therefore will not be included in the tabulations which are to follow. It should be mentioned, however, that the patient had electrophoretically the sickle cell trait in association with a severe, chronic hemolytic anemia, spherocytosis, splenomegaly and ulceration of the legs. Following splenectomy the anemia and jaundice subsided and the leg ulcers healed, but spherocytosis and the sickling phenomenon persist.

Although patients who have sickle cell anemia greatly outnumbered patients with variant forms of sicklemia in our clinic, no patient with sickle cell anemia was encountered who was over the age of 40 and few were over 30 years of age; on the other hand, 8 of the patients with other forms of sickle cell disease were over 40 and one lived to be 75.

Age at onset of illness: The onset of the illness is considered to be the time at which any of the manifestations of sicklemia with which we are familiar first became evident (Fig. 1). Anemia and acute episodes of either bone and joint pain or abdominal pain occurred before the age of 10 in every patient with sickle cell anemia. Of the 16 patients in the S-C group, 7 had experienced similar episodes during the first decade, and 2 others developed hip pain and disability at the age of 15. Four patients of this group experienced the first manifestations of disease during early adult life, one was asymptomatic until age 70 and one patient remains asymptomatic at age 65. Another patient with sickle cell-hemoglobin C disease, who was accidentally killed at age 15, had had only mild and fleeting pains in the legs which may or may not have been related to his sicklemia. Of the patients in this S-C group who had anemia and other symptoms in childhood, only 2 continued to have crises for more than 2 or 3 years in succession, and only 2 others subsequently developed in adult life episodes which were like the crises of sickle cell anemia.

Of the 4 patients with sickle cell-thalassemia, all developed bone and joint

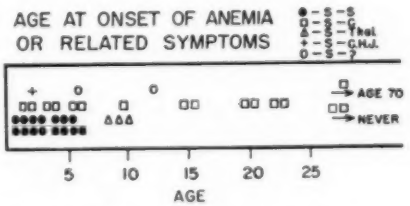


FIG. 1. Age of onset of the sickle cell diseases is taken to be the earliest time at which any of the features of sicklemia were noted by the patient or the physician. Note that sickle cell anemia and sickle cell-thalassemia disease invariably began during childhood, whereas the onset of the disease was often delayed in sickle cell-hemoglobin C disease.

pain in childhood. Of the 2 unclassified patients, one had "rheumatism" in childhood and after 25 asymptomatic years had severe abdominal crises without anemia. The other patient was first discovered to have anemia during early adult life but had no episodes of pain.

Habitus: The concept of the sickle cell habitus was evaluated in these patients by study of whole body photographs. All of the patients with sickle cell anemia had an asthenic habitus with disproportionately long legs, as illustrated in Figure 2. Most of the patients with the variant forms of sicklemia, in contrast, had a rather stocky build without leg-trunk disproportion. One patient in the S-C group rather closely resembled the patients with sickle cell anemia in body configuration. This patient had a more severe and protracted series of crises during childhood and adolescence than any of the other patients with sickle cell-hemoglobin C disease. The habitus of the patients with sickle cell-thalassemia was not unlike that of the S-C group.

Leg ulcers: Chronic ulcerations involving the maleolar area of the legs were found in six of the fifteen patients in the S-S group. None of those in the S-C, the S-thal or the unclassified groups were similarly involved. However, in the patient with sickle cell-congenital hemolytic jaundice, leg ulcers were present for many years but healed rapidly after splenectomy. It is of interest that another negro patient followed in our clinic who had congenital hemolytic jaundice also had leg ulcers as did a negro with thalassemia major. Neither of these patients had sicklemia. Such ulcers are only rarely encountered in white individuals with these diseases, and their occurrence in this group of negro patients raises the question of whether negroes may be predisposed to leg ulcers in association with various types of congenital hemolytic anemia.

Eyes: Tortuosity of the retinal veins, described as a frequent feature of sickle cell anemia, was seen in all but one of the patients in the S-S group, but in only 3 patients of the other groups. Of these 3, 2 were cases of sickle cell-hemoglobin C disease and 1 of sickle cell-thalassemia. Two of these patients showed evidences of arteriosclerotic vascular disease. Three patients of the S-C group had one or more episodes of intra-ocular hemorrhage. In one patient the hemorrhage was associated with recurrent tuberculous uveitis. A second patient had gross hemorrhage into the right eye following severe trauma, but 10 years later spontaneously developed a hemorrhage into the vitreous of the left eye, without apparent trauma. This patient had no other evidence of abnormal bleeding. The third patient of this group who had intra-ocular hemorrhage was noted to have a peculiar group of aneurysmal dilatations of the vessels in the region of the macula of the right eye and one year later developed massive vitreous hemorrhage, at which time a similar group of lesions was seen in the other eye. This patient has also had recurrent hematuria.

Heart: Klinefelter (25) and others have repeatedly emphasized the fact that cardiomegaly and various cardiac murmurs are present in almost all patients

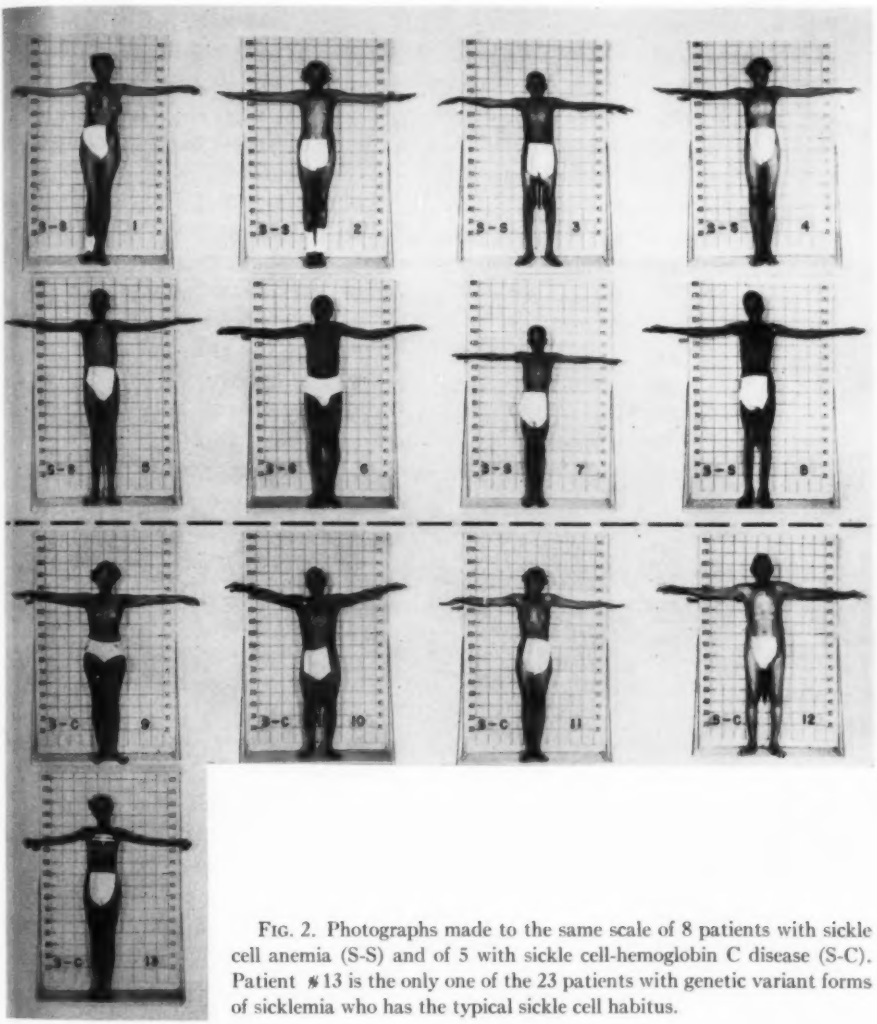
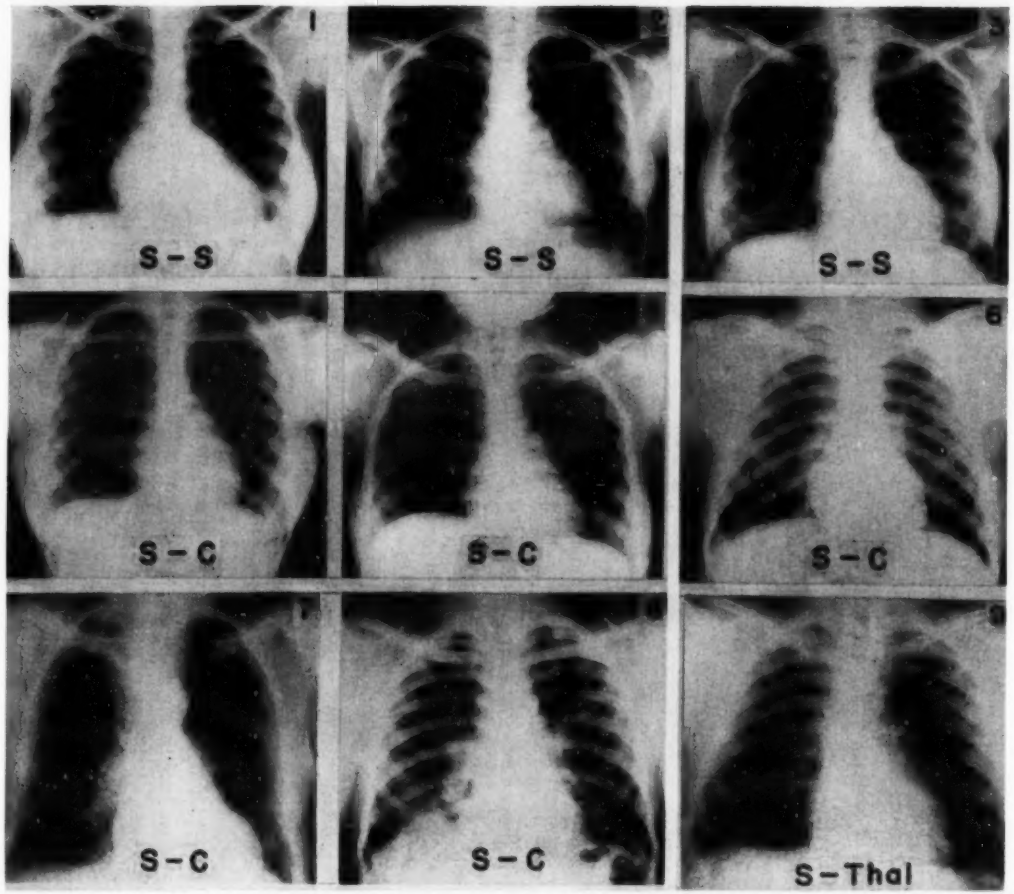


FIG. 2. Photographs made to the same scale of 8 patients with sickle cell anemia (S-S) and of 5 with sickle cell-hemoglobin C disease (S-C). Patient #13 is the only one of the 23 patients with genetic variant forms of sicklemia who has the typical sickle cell habitus.

with sickle cell anemia, and that the occurrence of inflammatory joint manifestations concurrent with cardiac abnormalities very frequently suggests a diagnosis of rheumatic fever. Of the 15 patients in the S-S group 12 had been thought at one time to have rheumatic heart disease. The heart was seen to be enlarged and of a globular configuration in all 15 (Fig. 3), an apical systolic murmur had been described in all, and 7 of the group had developed transient first degree heart block. Electrocardiograms in this group were otherwise



Sickle cell anemia (#1, #2, #3). Note moderate dilatation of the right heart and left ventricle with possible minimal dilatation of the left atrium.

Sickle cell-hemoglobin C disease (#4, #5, #6, #7, #8). Note the heart size is within normal limits but suggests minimal dilatation. Numbers 5 and 6 are in the third trimester of pregnancy. Number 7 has hypertension, and number 8 has Boeck's sarcoid.

Sickle cell-thalassemia disease (#9). Note minimal dilatation of the heart with moderate enlargement of the left ventricle. The patient had hypertension.

FIG. 3.Standard six-foot chest roentgenograms of patients with sickle cell diseases. Patients were selected from each group to show variation within the group.

normal. In contrast, there was only slight evidence of cardiomegaly in patients with the sicklemia variants except in 3 who also had essential hypertension. In 6 of the patients with S-C disease apical systolic murmurs were heard but none was impressive enough to suggest valvular heart disease. One patient of this group developed fever, tachycardia, and frequent ventricular extrasystoles and the diagnosis of rheumatic fever with carditis had been considered but this diagnosis was not suggested in any of the other patients of the sicklemia variant groups. Twenty patients in the variant groups had electrocardiograms. Except for extrasystoles in the case mentioned, transient first degree heart block in a patient with sickle cell-thalassemia disease, and left axis deviation in an elderly hypertensive patient with sickle cell-hemoglobin C disease, no abnormalities were noted.

Lungs: Patients with sickle cell anemia not infrequently developed episodes of pneumonitis not specifically attributable to infection, in some instances probably resulting from pulmonary infarction. Episodes of pneumonitis have been much less frequent in the patients of the sicklemia variant groups, and in only 2 instances were pulmonary infarctions suspected. One patient in the S-C group had multiple pulmonary emboli associated with thrombophlebitis following delivery, and the other, a 35 year old man who also had S-C disease developed pleuritic pain following thrombophlebitis in the leg.

Liver: A detailed study of the state of the liver in patients with sicklemia was recently made in this clinic and included many of the patients in the present report (3). In sickle cell anemia progressive hepatic enlargement and impairment of hepatic function were frequently found. In cases of atypical sickle cell disease evidence of hepatic dysfunction was much less marked. Only 5 of the 23 patients with genetic variants of sickle cell disease included in the present report, 3 in the S-C group and 2 in the S-thal group, had palpable enlargement of the liver. In no case was there evidence of severe liver dysfunction.

Spleen: Presumably as a result of repeated splenic infarctions and consequent fibrosis, the spleen in patients with sickle cell anemia is seldom palpably enlarged past the first few years of life and has never been found enlarged after the age of ten in any of our group of patients with this disease. Rather, the finding at autopsy of an exceptionally small spleen, not infrequently weighing less than ten grams, is the rule in this disease. In one of our S-S patients splenomegaly was last noted during a crisis at age 9. In all others the spleen was either not palpable at any time or had become small at an earlier age. In contrast, splenomegaly has been a usual feature of previously reported cases of sickle cell-hemoglobin C disease, and in 9 of the 16 patients in our group this organ was palpably enlarged. No clear cut correlation between age or severity of disease and degree of splenic enlargement was possible. In a patient who had recurrent and frequent crises from childhood the spleen remained easily palpable at age 16. Crises were associated with transient increase in size of an

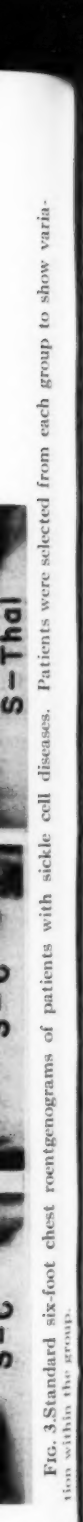


FIG. 3. Standard six-foot chest roentgenograms of patients with sickle cell diseases. Patients were selected from each group to show variation within the group.

FIG. 4. An oblique roentgenogram with barium in the colon shows a large spleen shadow with spotty calcifications. The patient was a 75 year old negro man who had sickle cell-hemoglobin C disease. The spleen was easily palpable and at autopsy weighed 250 grams. See text for further details.

already palpably enlarged spleen in 3 patients, and in a fourth this organ was felt only during such an episode. Two patients who have been repeatedly examined have been observed to develop progressive enlargement of the spleen. The persistence of splenomegaly in this S-C group is emphasized by the finding of a large spleen in a man 75 years old (Fig. 4), and in the second oldest patient of the group, a woman of 65. On the other hand, a fibrotic spleen weighing less than 40 grams was found at autopsy in each of two patients with S-C disease who died of post partum hemorrhage, yet the clinical courses of the two were dissimilar. One had been asymptomatic but for a crisis with each of 2 pregnancies, while the other had rather severe disease first as a child. Two patients with splenic enlargement had one episode each of pain of pleuritic character in the region of the spleen, quite possibly due to splenic infarction.

Recently Cooley and his associates (25a) have described the occurrence of splenic infarcts during aerial flights in negroes with sicklemia. In 5 of their 6 cases the spleen was enlarged, and an appreciable degree of anemia was present in only two. It seemed likely to us that at least some of these patients had

sickle cell-hemoglobin C disease. Through the courtesy of Major S. P. Wise, Captain R. B. Breitenbucher, and Captain J. P. Doenges, Fort Jackson, South Carolina, we were able to obtain blood from a 19 year old negro soldier who had developed splenic infarction while flying. He had been demonstrated to have sicklemia and moderate anemia. Electrophoretic examination of the hemoglobin showed that he has sickle cell-hemoglobin C disease.

Microscopic examination of 2 very small spleens removed from adult patients with sickle cell-hemoglobin C disease at autopsy revealed extensive scarring with hemosiderin deposition in the fibrous bands. Normal splenic architecture was nowhere seen and the pulp was densely packed with red blood cells. This picture is indistinguishable from that seen in cases of sickle cell anemia. The spleen of another patient of the S-C group who died at age 75, weighed 250 grams, was also scarred and had extensive hemosiderin deposits. There were no malpighian bodies seen. It was the opinion of the pathologist that the picture described was similar to that which is often seen in children with sickle cell anemia.

Of the 4 patients with sickle cell-thalassemia disease, one had an easily palpable spleen at age 34, while in two other adult patients the spleen had never been felt despite repeated examinations. The fourth patient was subjected to splenectomy at age 34 at which time a small, fibrotic spleen and sixteen accessory spleens were removed, none of which had been palpable. Of the patients considered to have unclassified sicklemia, splenomegaly was present in both, although in one this organ was not palpated but was described as enlarged at the time of an exploratory laparotomy.

Kidneys: Occasionally patients with sickle cell anemia develop a peculiar nephritis which may lead to uremia and death. None of the patients in any of the groups considered here showed this nephritis, but one in the S-C group who had previously had a left nephrectomy because of recurrent, gross hematuria now has a persistent mild albuminuria without hypertension.

Episodes of gross, renal hematuria are well known to occur in individuals with sicklemia (26, 27). Goodwin, et al. (27) reported seven cases in which unexplained, gross, unilateral renal hematuria occurred in association with the sickling phenomenon. Four of these patients were available to us for restudy; two were found to have the sickle cell trait, one sickle cell anemia, and one sickle cell-hemoglobin C disease. Of the 15 patients of the S-S group one had a single episode of hematuria, while three patients in the S-C group, including the one from Goodwin's series, had gross hematuria. Two of these have had many recurrences, and in one nephrectomy had been performed with repeated recurrence of the hematuria since the removal of the kidney. One patient with sickle cell-thalassemia had a single episode of hematuria. This was a 27 year old negro woman who also had an unexplained subarachnoid hemorrhage.

Bones and joints: The crises of sickle cell anemia are frequently associated

with multiple joint pains with or without evidences of inflammation. Aching pain over the long bones occurs with only slightly less frequency. Hydrarthroses are occasionally seen. In a small percentage of the episodes of bone pain, localized inflammatory changes involving the periosteum and the soft tissues are found. In our S-S group periodic episodes of joint pain which suggested acute rheumatic fever occurred in every case, while hydrarthroses have been found in only 3. These patients also had had many episodes of mild, generalized bone pain. Of the 16 patients in the S-C group 7 have experienced episodic joint pains which suggested rheumatic fever. While individual attacks have been quite severe, the frequency of these attacks has been much less than in those of the S-S patients. Hydrarthrosis occurred in one patient of the S-C group, and in none of the S-thal or unclassified sicklemia groups.

Radiologic findings in the bones of patients with sickle cell anemia were, in general, similar. These included a slight diminution in density of all the bones visualized, a coarsening of the bony trabeculation which was particularly constant in the vertebrae, and in most instances a "fish mouth" appearance of the inter-vertebral margins. In addition there were scattered areas which suggested old infarction in the long bones, and a finely mottled appearance of the skull. Such changes were rarely impressive in the genetic variants and were noted in only 4 patients of these groups. The bones of one patient with sickle cell-hemoglobin C disease seemed generally osteoporotic and contained numerous small areas of sclerosis which suggested previous infarctions, and a second patient had several similar areas suggestive of bone infarction. In one patient with sickle cell-thalassemia there was a very slight coarsening of trabeculation of the vertebrae and possibly some increase in density of the long bones. One patient with unclassified sicklemia showed coarsening of the trabeculation of the vertebrae, ribs and long bones and cortical irregularity in the long bones.

Four of the 16 patients with sickle cell-hemoglobin C disease were found to have osteochondritis of the femoral capital epiphyses apparently due to aseptic necrosis. A fifth had a similar process in the right humeral head (Fig. 5). This is a surprising observation since none of the patients with sickle cell anemia in our clinic have shown these lesions. Two of these 5 patients were females in their third decade, both of whom developed hip pain during childbearing age. In one of these the evidences of aseptic necrosis were present bilaterally, and the other had marked changes in one hip with early or minimal evidence of bone necrosis in the other. A third patient was a male who developed symptoms suggestive of Legg-Perthe's disease at age 10 or 11 with radiologic evidence of destruction of the left femoral capital epiphysis. This patient was subsequently followed in the Children's Hospital School of Baltimore, and at age 15 developed apparent Perthe's disease of the right hip. His course has been considered atypical for Perthe's disease because of the poor response to treat-

ment, the late onset, and because it is found that of several hundred cases of Perthe's disease which have been seen in that hospital, this patient is the only negro. Reference to the film museum of the Department of Radiology in the Johns Hopkins Hospital revealed an interesting case of obscure avascular necrosis of the femoral head. This patient was a negro male 22 years old who had had bouts of "rheumatism" as a child with pain and limitation of motion in the hips for 2 years. A blood study had revealed a hematocrit of 35 per cent and many target cells were seen on the blood smear. It is suggested that this man might well have sickle cell-hemoglobin C disease, and attempts are being made to reestablish contact with him.

Robinson and Sarnot (28) reported the occurrence of increased mandibular and maxillary radiolucency with coarsening of the trabecular pattern in patients with sickle cell anemia. A survey of dental findings in patients with sicklemia is under way in this hospital. Preliminary observations confirm the findings of these authors and suggest that a distinction can be made between the S-S and the S-C groups on the basis of much more extensive changes in the former group than in the latter (Fig. 6). That these bone changes are not specific, however, is proved by their presence in one case of congenital hemolytic anemia without demonstrably abnormal hemoglobins. A detailed report of this dental survey will be published separately from the Dental Clinic of the Johns Hopkins Hospital.

Abdominal pain: Abdominal pain as a manifestation of crisis in sickle cell anemia is common and had occurred in 14 of the 15 patients of the S-S group. In 4 of these the pain was severe enough to suggest an acute surgical emergency. Of the S-C group, 4 had recurrent abdominal pain but only 2 had episodes in which severe pain and rebound tenderness in the presence of sicklemia caused uncertainty as to the true nature of the disorder. One patient proved to have acute appendicitis, the other had a normal appendix removed. In one patient with unclassified sicklemia, however, severe abdominal pain has been the major symptom and led on 3 occasions to exploratory laparotomy. In none of the patients with sickle cell-thalassemia has abdominal pain been a feature of the disease.

Central nervous system: Various neurological manifestations of cerebral vascular occlusion due to intravascular sickling are well recognized but have been relatively uncommon in the patients reported here. One patient of the S-S group during childhood had a transient episode of mental confusion and hemiparesis which was attributed to cerebral vascular thrombosis. Two patients in the S-C group had a series of generalized convulsions attributed to a similar phenomenon. One negro patient with sickle cell-thalassemia developed severe pain and weakness in the legs at age 27. Prior to this episode she had had only mild, intermittent episodes of bone pain. There was pronounced atrophy of

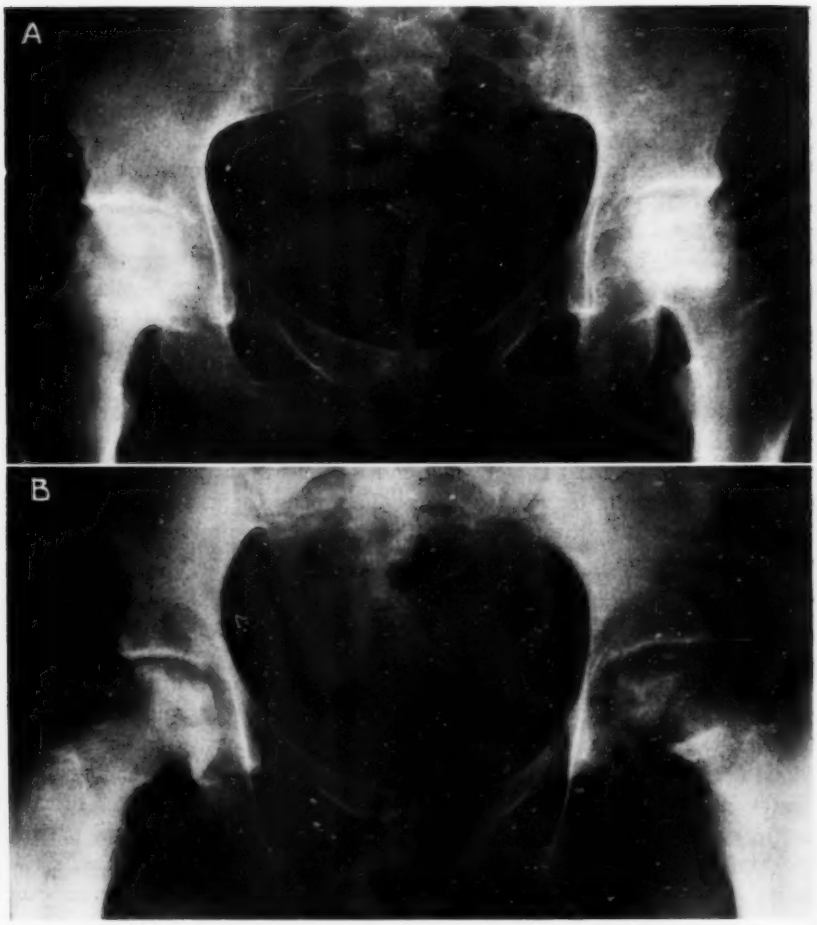


FIG. 5. *Aseptic necrosis of the femoral heads in sickle cell-hemoglobin C disease.* (A) Bilateral osteochondritis, probably revascularized and repaired. This roentgenogram was made 3 years after hip pain had developed at age 20 (Case #12).

(B) This film was made approximately one year after the patient first complained of hip pain, (Case #13). Note the punched out lesions in the right hip and a greater degree of bone irregularity and destruction of the left. These changes probably reflect early stages of repair after revascularization.

(C) Roentgenogram of a negro boy, (Case #8), made at age 14. Hip pain had developed approximately 4 years earlier. Note the destructive changes in the left femoral capital epiphysis and the apparently normal right femoral head.

(D) Same patient as in (C) two years later has evidence of destructive changes in the right hip and of repair of the left.

(E) Same patient as in (C) and (D) at age 18 shows repair with some deformity of both hips.

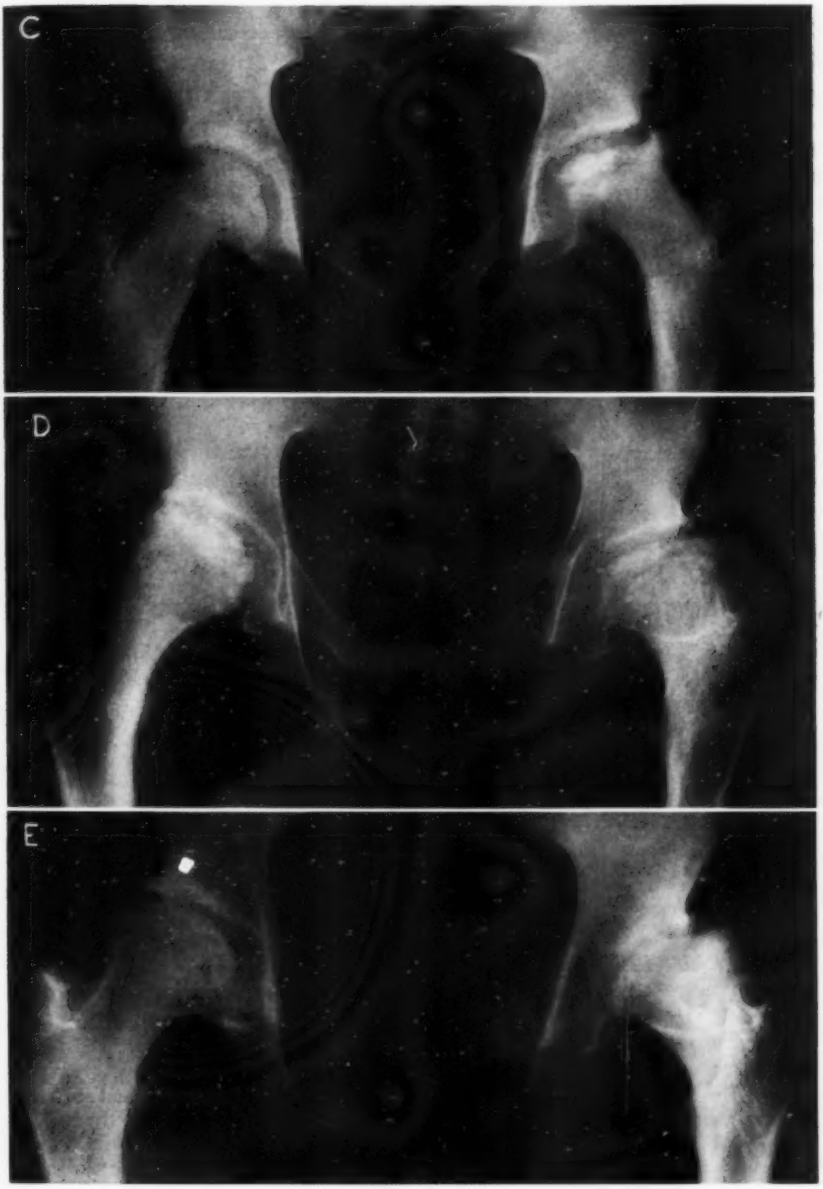


FIG. 5.

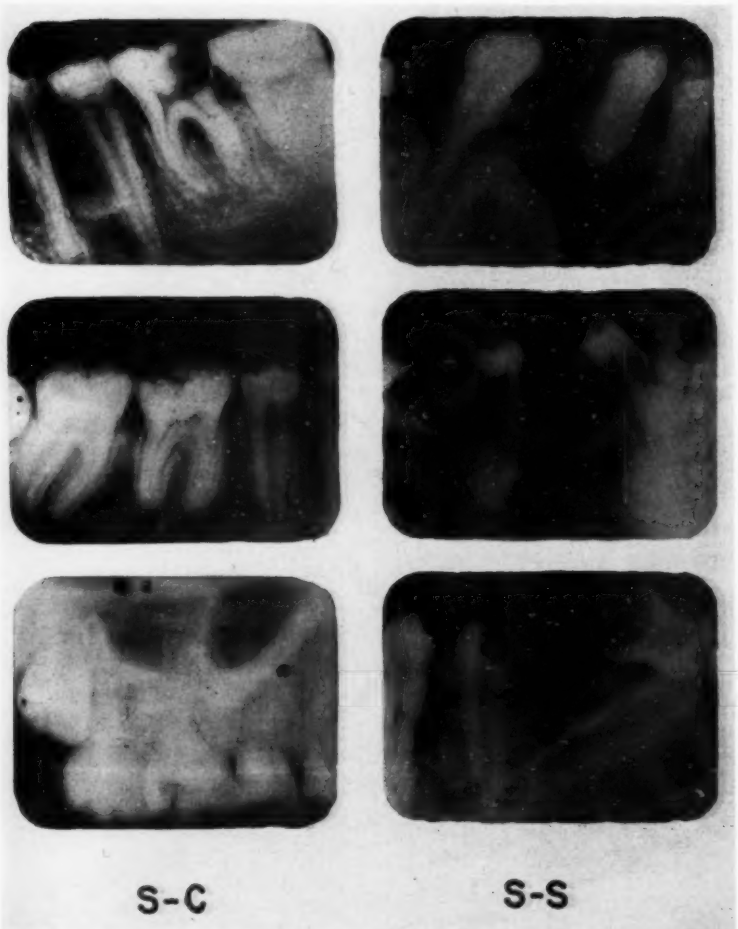


FIG. 6. *Dental films of patients with sickle cell diseases.* The three views on the left are from a patient with sickle cell-hemoglobin C disease. Note spotty areas of translucency and relatively coarse trabeculations.

The three views on the right are from a patient with sickle cell anemia. Note the marked translucency and lacy trabecular pattern of almost all of the bone. (Dental films were supplied by Dr. Joseph R. Prowler of the Johns Hopkins Hospital Dental Clinic, and are from a series which he is preparing for publication.)

the muscles of the lower extremities and biopsy showed hyalinization of some muscle fibers. She was found to have sub-arachnoid hemorrhage and while under observation she developed a mild hemolytic crisis.

Pregnancy: The occurrence of pregnancy in patients with sickle cell anemia

has been considered to be a problem of considerable magnitude because of severe obstetrical complications, often leading to fetal or maternal death (29, 30). Anderson and Busby (31) found that in the Johns Hopkins Hospital from 1928 to 1948 there were 17 pregnancies in 11 patients with sickle cell disease with no maternal deaths and 4 infant deaths. Hemolytic episodes were said to have occurred in 4 of these women, one just prior to delivery and the other 3 immediately post-partum. Since 1948 several patients with sickle cell anemia have had successful pregnancies, and there have been no infant or maternal deaths associated with this disease. Included in the present series are 5 females of the S-S group who have become pregnant on one or more occasions. In the course of most of these pregnancies whole blood transfusions were administered to correct the existing anemia, but in no instance was there a severe exacerbation of the disease in association with the pregnancy.

On the other hand, of the 8 females in the S-C group, 5 have had one or more pregnancies, and in every instance there was a marked increase in the degree of hemolytic anemia often associated with other manifestations of crisis during the last trimester of pregnancy or in the immediate post-partum period. Three of these patients had never had symptoms of their disease prior to the onset of pregnancy, and a fourth had been asymptomatic for the preceding twelve years. Since the report of Anderson and Busby there have been two maternal deaths associated with sicklemia in this hospital, and a third death occurred in the patient's home during the twenty-ninth week of gestation. Two of these patients were proved to have had sickle cell-hemoglobin C disease, and the third had a clinical course and hematologic pattern which indicates that she too had this disorder. Two of the deaths were related to post-partum hemorrhage, while the cause of sudden death in the third was not established. The one female of the unclassified sicklemia group had a history of hemolytic anemia becoming clinically manifest during each of 2 pregnancies with no intervening symptoms referable to the sicklemia.

Hematologic findings: RED CELLS: In classical sickle cell anemia a moderately severe degree of anemia is constantly present. Only two patients among a large number in our clinic files have been exceptions to this generalization. These two patients were studied in periods when no anemia was present, but in no other patient with sickle cell anemia was the hematocrit ever found to exceed 30 per cent (Fig. 7). In contrast, a hematocrit value of 30 per cent was exceeded by every patient with a variant form of sicklemia, and most of these patients were free of anemia during asymptomatic intervals. Despite the generally mild degree of hemolytic activity which characterized the patients with sickle cell-hemoglobin C disease, very severe hemolytic crises were occasionally encountered. In three of these patients the hematocrit became as low as 20 per cent and in two others as low as 13 per cent during crisis. In 3 of the patients with sickle cell-thalassemia, anemia was present frequently during asymptomatic

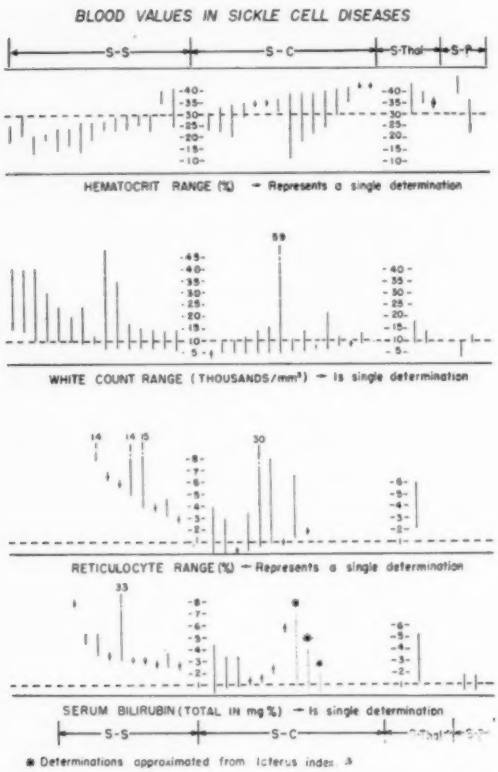

BLOOD VALUES IN SICKLE CELL DISEASES
S-S
S-C
S-Thal
S-P
HEMATOCRIT RANGE (%) — Represents a single determination
WHITE COUNT RANGE (THOUSANDS/mm³) — Is single determination
RETICULOCYTE RANGE (%) — Represents a single determination
SERUM BILIRUBIN (TOTAL IN mg %) — Is single determination
* Determinations approximated from Icterus index

FIG. 7. Graphic representation of various hematologic values of patients with sickle cell diseases. The lines on the chart connect highest and lowest values but do not suggest a mean for many determinations. The dotted line at the 30 per cent hemoglobin level is arbitrary. Other dotted lines represent the approximate upper normal limit.

intervals as well as during crises, but was of a milder degree than in sickle cell anemia and severe hemolytic crises did not occur. The one negro patient with this disorder has been observed in one hemolytic crisis, the hematocrit falling from 41 to 32 per cent. One patient with unclassified sicklemia maintained a normal hematocrit during severe episodes of abdominal pain and has only transiently had mild anemia. The other patient in this group became anemic only with her first pregnancy.

Abnormalities of the blood smear were present in all of the patients studied. Smears from most patients with sickle cell anemia were characterized by red cells of normal size and color, some sickled cells and approximately 5 per cent target cells. However, some individuals with this disorder showed hypochromia,

anisocytosis, poikilocytosis, many sickled cells and as many as 25 per cent target cells. Blood smears from patients with sickle cell-hemoglobin C disease invariably had greater than 50 per cent and in some cases nearly 100 per cent target cells. Sickled cells were seen on smear in only a few of the patients. Smears from 2 of the 4 patients with sickle cell-thalassemia showed marked hypochromia, great variation in cell size and shape, polychromatophilia, basophilic stippling and approximately 40 per cent target cells. The other two patients of this group had only mild hypochromia, polychromatophilia and approximately 20 per cent target cells. Of the 2 patients with unclassified sicklemia, one had the characteristics of sickle cell-thalassemia, i.e. marked hypochromia, anisocytosis, oval forms, polychromatophilia, and basophilic stippling, and the smear of the other patient differed from normal only by the presence of approximately 20 per cent target cells. Spherocytes were seen only in the patient with sickling and congenital hemolytic jaundice.

Reticulocyte counts on the blood of patients with sickle cell anemia were invariably greater than 1 per 100 red cells, whether in crisis or during an asymptomatic interval (Fig. 7). A reticulocytosis of 3.5 per 100 red cells was present in one patient with this disease even though the hematocrit was 40 per cent at the time. Despite the fact that data on reticulocyte counts in the variant forms of sicklemia were not so numerous as in cases of sickle cell anemia, many of the counts that had been obtained were normal. The serum bilirubin concentration was invariably elevated in patients with sickle cell anemia and was frequently found to be normal in patients with the various other forms of sicklemia.

LEUCOCYTES: Leucocytosis, predominantly polymorphonuclear, is a usual finding during a crisis and not infrequently persists during asymptomatic periods in patients with sickle cell anemia. Thirteen of the 15 patients with sickle cell anemia had at some time in their course a leucocyte count of less than 10,000 per mm.^{3} although the majority of counts in all of these patients had been considerably elevated. Two patients of this group who had the most severe chronic anemia were never found to have a normal leucocyte count. Patients with sickle cell variants usually had leucocyte counts of less than 10,000 per mm.^{3}, although on occasion extremely marked leucocytosis developed during a crisis. One patient with sickle cell-hemoglobin C disease developed a leucocyte count of 22,000 per mm.^{3} during a severe hemolytic crisis, and another patient who probably had this disease developed leucocytosis to 59,000 per mm.^{3} during a hemolytic crisis associated with pregnancy.

DISCUSSION

The concept of sickle cell disease has been broadened in recent years to include disorders caused by the inheritance of a gene for sickling together with

a gene determining an unrelated red cell abnormality. Individuals with this mixed genetic background display the sickling phenomenon in conjunction with evidences of a peculiar hemolytic disorder which is evidently the result of interaction of the two abnormal genes. Until a few years ago such cases were not differentiated from sickle cell anemia, giving rise to the belief that the clinical manifestations of sickle cell anemia are more variable than we now recognize them to be. With the knowledge and methods currently available, it is possible to segregate individuals with sicklemia on the basis of their genetic constitution. In this way the clinical features of each genetic group can be appraised. A variety of gene combinations are theoretically possible and several have been identified. It seems likely that others will be recognized in the course of future studies.

In the present study 24 patients who were heterozygous for the sickling phenomenon were recognized to have inherited an additional and unrelated red cell abnormality. These cases, together with 19 others collected from the literature, provide an opportunity to draw tentative conclusions concerning clinical aspects of the genetic variants of sicklemia. It is apparent that in every case the variant disorder pursued a course which was atypical with respect to sickle cell anemia.

Sickle cell anemia appears to be a disease with certain remarkably constant clinical features. At the Johns Hopkins Hospital only two patients with proven sickle cell anemia have been encountered whose clinical course varied from that expected of patients with this disease. With the exception of these two patients, both of whom had prolonged remissions during which anemia entirely subsided, anemia was apparent in childhood and constantly present throughout life. Jaundice was unremitting. Typical crises of bone and joint or abdominal pain were frequent, and cardiac abnormalities related to the chronic anemia were almost invariable. All of the patients studied displayed a peculiar aberration of the body habitus. Other abnormalities such as chronic leg ulcers, tortuosity of the retinal vessels and X-ray evidence of diffuse bone disorder were often seen. The virulence of the disease is indicated by the short duration of life of these patients.

The disorders presented by the 43 patients with variant forms of sicklemia were in general much milder than sickle cell anemia. Virtually all of the manifestations of sickle cell anemia were seen at one time or another in the variant group, but they were less frequent and less severe. In addition, certain manifestations which were not encountered in sickle cell anemia were prominent in the variant cases.

Anemia was discovered in childhood in only 21 of the 43 cases of variant sicklemia. Even in those cases in which anemia was encountered in early life, normal hemoglobin values were often observed subsequently. Anemia of appreciable degree was present episodically in patients with sickle cell-hemo-

globin C disease, and these episodes were generally infrequent. Some patients with this disease have never been known to be anemic. Sickle cell-thalassemia disease was also characterized by periodic episodes of anemia but in this disorder the episodes appeared to occur more frequently than in sickle cell-hemoglobin C disease. In the variant cases jaundice often subsided and the serum bilirubin concentration was normal when anemia was not pronounced. The persistent normoblastic hyperplasia of the bone marrow at these times suggests that a mild degree of hemolytic activity continued, even in the absence of anemia. This observation is supported by the demonstrated short life span of the red cells (32). Patients with sicklemia who have had at any time a hematocrit value in excess of 30 per cent should be suspected of having a disorder other than sickle cell anemia. On the other hand it is important to note that patients of the variant group may have transient hemolytic episodes during which profound anemia develops. Such episodes were observed in four of our cases of sickle cell-hemoglobin C disease. During hemolytic crises patients of the variant groups displayed reticulocytosis and at times extraordinary numbers of nucleated red cells appeared in the blood. In asymptomatic intervals the reticulocyte count was usually within the normal range, contrasting with the persistent reticulocytosis of sickle cell anemia. Marked leukocytosis often accompanied crises in the variant cases, but sustained elevation of the white count, so frequently encountered in sickle cell anemia, did not occur.

Striking differences in the appearance of the red cells were important in differentiating the several genetic variants. Sickled erythrocytes were often seen on the stained blood smears of patients with sickle cell anemia and were occasionally noted in the variant groups. Spherocytosis was observed only in the patient with sickle cell-congenital hemolytic jaundice. Hypochromia and microcytosis were usual features of sickle cell-thalassemia but were not of sufficient degree and specificity to be pathognomonic. The most impressive difference between the groups was in the number of target cells, a point which has been emphasized by Kaplan, Zuelzer and Neel (32). The original description of sickle cell-hemoglobin C disease included the observation that more than 50 per cent target cells were seen in the blood smears of patients with this disorder (9). Twenty-six of the 27 cases of sickle cell-hemoglobin C disease reviewed in the present report showed more than 50 per cent target cells, and in some cases the number approached 100 per cent. Although such a high percentage was seldom encountered in patients with sickle cell-thalassemia, target cells in this disease were more numerous than in sickle cell anemia or in thalassemia major. Because of the numerous target cells seen in the blood of patients with homozygous hemoglobin C disease (13, 33), one would suspect that hemoglobin C predisposes to target cell formation. The high incidence of target cells in sickle cell-thalassemia is not so readily explained.

The spleen may be enlarged in patients with sickle cell anemia during the

first few years of life, but thereafter it undergoes an atrophic change and becomes progressively smaller. Palpable enlargement of the spleen was not observed in any of our cases of sickle cell anemia after the age of nine. In contrast, 30 of the 43 patients of the variant groups had splenomegaly, including 8 of 11 cases of sickle cell-thalassemia and 20 of 27 cases of sickle cell-hemoglobin C disease. In some cases progressive enlargement of the spleen was observed to occur even in adult life, and transient increase in size was noted during hemolytic crises. Haden and Evans (34) reported that splenectomy in two white patients with "sickle cell anemia" associated with splenomegaly had been followed in one by an unexpectedly mild course. In these and in other similar cases (35), it seems likely in retrospect that the patients had genetic variants of sicklemia. Splenectomy in a proven case of sickle cell-hemoglobin C disease was without beneficial effect (13). On the other hand, removal of the spleen from the patient with sickle cell-congenital hemolytic jaundice was followed by immediate subsidence of anemia. In this case there was no evidence of interaction between the two abnormal genes and the patient appeared merely to have the sickle cell trait superimposed upon typical congenital spherocytosis.

Crises similar to those encountered in sickle cell anemia occurred in patients with the variant diseases, but with much less frequency. Abdominal pain was rare in the variant groups. Only one of the patients proved to have sickle cell-hemoglobin C disease, and none with sickle cell-thalassemia had episodes of abdominal pain simulating an intraabdominal surgical disorder. One patient who remains unclassified as to his genetic make-up was subjected to laparotomy on three occasions because of recurrence of severe abdominal pain. Bone and joint pain occurred in almost half of the patients with sickle cell-hemoglobin C disease and in all of those with sickle cell-thalassemia. In the former group attacks of pain were infrequent in childhood and rare in adult life. In the latter group bone and joint pain was a regular feature of crisis and occurred at intervals throughout life.

Disproportionate elongation of the extremities, so common in sickle cell anemia, was observed in only one of the variant cases. X-ray evidence of abnormal trabeculation of bone was regularly seen in patients with sickle cell anemia, and bone infarcts were often demonstrable. These lesions were extremely mild or absent in the variant groups. On the other hand, aseptic necrosis of the humeral or femoral heads was present in 9 of the variant cases, including 6 of the 27 with sickle cell-hemoglobin C disease and 3 of the 11 with sickle cell-thalassemia. So far as we know, these lesions have not been found in any case of proven sickle cell anemia. Reich and Rosenberg (36) were the first to relate aseptic necrosis of the capital epiphyses to genetic variants of sicklemia. They found three patients with sickle cell-thalassemia in whom aseptic necrosis had been previously noted but had been thought to be attributable to other causes. Their report includes the description of a similar

lesion in a patient considered to have sickle cell anemia, but who was described as having numerous target cells in the blood smear and a palpable spleen. It seems likely that this patient also had a genetic variant of sicklemia. Ehrenpreis and Schwinger (37), Hamburg (38) and Legant and Ball (39) have reported a total of six cases in which aseptic necrosis of the femoral or humeral heads was associated with what was thought to be sickle cell anemia. Adequate descriptions of these cases are not available, but the patient described by Hamburg had a disorder which was clearly atypical for sickle cell anemia and probably represented one of the variants. More recently Moseley and Manly (41) have reported the occurrence of aseptic necrosis of the femoral or humeral heads in 5 patients with sicklemia. Although detailed clinical descriptions are not provided, the information available suggests that all of these cases were atypical for sickle cell anemia.* If one assumes that the bone necrosis is on the basis of vascular occlusion by sickled erythrocytes, it is difficult to understand why this lesion should be more common in the variant groups than in sickle cell anemia.

Abnormalities of the retina occurred with surprising frequency in our patients with sickle cell-hemoglobin C disease. Tortuous retinal vessels, so common in sickle cell anemia, were seen in only a few patients of the variant groups and in all but one were associated with arteriosclerotic vascular disease. However, three of the S-C patients had intra-ocular hemorrhages and a fourth developed unilateral optic atrophy. While it has not been definitely established that these retinal lesions were the result of the underlying blood disorder, their frequency and peculiar nature suggest this possibility in at least some instances. It seems quite probable that the optic atrophy was caused by syphilis which the patient was known to have. The hemorrhagic lesions are not so easily explained. In one patient, presumed retinal detachment and extensive hemorrhage into the vitreous followed trauma, but 10 years later similar hemorrhage occurred in the other eye without recognizable cause. Another patient was observed to have peculiar red spots along retinal vessels, giving the appearance of small aneurysmal dilatations rather than hemorrhage. A year later, the retina of this eye detached spontaneously and hemorrhage into the vitreous occurred. More recently, aneurysmal lesions have appeared in the other eye. It is of interest that this patient has also had repeated attacks of gross hematuria. The third patient had peripheral retinal detachment and recurrent uveitis, associated with marked cutaneous hypersensitivity to tuberculin. Phthisis bulbi developed and enucleation was necessary. Whether the red cell disorder was concerned in any way with the retinal detachment is unknown.

* Dr. Max M. Strumia and Dr. Lawrence Taylor, Hematology Clinic, Bryn Mawr Hospital, Bryn Mawr, Pa., have studied a negro patient who was thought to have atypical sickle cell anemia and Legg-Perthe's disease. Electrophoretic study of the hemoglobin of this patient, performed in our laboratory, shows that he has sickle cell-hemoglobin C disease.

TABLE I

Clinical and Hematologic Data of Twenty-Four Patients With Genetic Variants of Sicklemia in the Present Survey

CASE	HISTORY NUMBER	PATIENT (AGE, RACE, SEX)	GENETIC TYPE	AGE AT ONSET OF SYMPTOMS	HEMATOCRIT		CELL INDICES		RETICULOCYTES		TARGET CELLS %	SERUM BILIRUBIN		LEUCOCYTES × 1000/mm³		SPLEEN SIZE (0 to ++++)	CHARACTER OF CRISIS		HEMATURIA (0 to ++++)	ANEMIA WITH PREGNANCY	AVASCULAR NECROSIS OF HIPS	COMMENT
					High %	Low %	MCV	MCHC	High %	Low %		High mg. %	Low mg. %	High	Low		Abdominal	Joint				
1	628321	H.C. 37 CM	S-C	20	41	30	82	34	3.5	0.4	>50	3.4	1.1	22	7	+–++	0	0	++++	–	no	Detached retina since being reported as Case #1 by Smith (12).
2	611651	S.R. 16 CF	S-C	15	39	19	78	31			80	3.4	1.0	13	9	++	0	++	++	–	no	Reported as Case #2 by Smith (12).
3	—	R.R. 13 CM	S-C	never	39						>50	17*				++	0	0	0	–	no	Killed accidentally. Reported as Case #5 by Smith (12).
4	503965	T.N. 16 CF	S-C	2	40	25	79	33	3.0	0.1	>50	4.3	0.8	16	5	++	++	0	0	–	no	Reported as Case #6 by Smith (12).
5	459508	E.N. 19 CM	S-C	2	35	30	82	30			>50	2.1		14	5	0–+	0	++	0	–	no	Reported as Case #7 by Smith (12).
6	174945	G.W. 21 CF	S-C	18	33	23	88	34	6.6	1.4	60	25*	0.8	12	8	++	0	0	0	yes	no	Reported as Case #3 by Smith (12).
7	257485	B.B. 16 CF	S-C	2	39	22	84	36	4.0	0.0	80	30*	0.8	14	6	0	0	+	0	yes	no	Reported as Case #4 by Smith (12).
8	397494	G.N. 20 CM	S-C	3	43				2.0		>50	1.6		9.6		0	0	++	0	–	yes	Well except for hip pain present since age 10.
9	599312	M.H. 65 CF	S-C	never	36	35	74	31			80	1.4		9		+	0	0	0	–	no	No symptoms at any time
10	354466	J.C. 75 CM	S-C	70	30	24	83	36	2.0	1.1	60	2.1	1.0	10	5	+++	+	0	0	–	no	Anemia discovered on routine examination at age 70.
11	245466	E.D. 14 CM	S-C	4	37	31				0.4	50		7.5*	9	5	+	++	++	0	–	no	Appendectomy at age 6, normal appendix.
12	281428	H.H. 27 CF	S-C	24	35	22	88	33			>50			8	7	0	0	+	0	yes	yes	Severe hemolytic episodes only with pregnancy. Died of post-partum hemorrhage. Reported as Case #42 by Green (3).
13	127304	D.J. 25 CF	S-C	2	34	21	84	32	8.	1.0	>50	5.9	2.1	12	5	0	++	++	++++	yes	yes	Hemolytic episodes with pregnancy. Died of post-partum hemorrhage. Reported as Case #43 by Green (3), and Case #3 by Goodwin (27).

14	112606	E.F.	40	CM	S-C	10	42	36	88	30			>50			11	6	0	0	++	0	—	no	Intra-ocular hemorrhage.
15	170973	W.K.	52	CM	S-C	15	39	28					>50			7	4	0	0	++	0	—	yes	Well except for hip deformity.
16	221373	E.K.	37	CF	S-C	15	36	32				0.2	>50		5*	9	4	0	0	+	0	no	yes†	Convulsive seizures, intracranial hemorrhage.
17	305141	E.F.	27	CF	S-C probable	23	39	12	79	29	30	0.6	>50	3.6		39	5	+++	0	0	0	yes	no	Hemolytic anemia only with pregnancy. Died home, pregnant. Reported as Case #41 by Green (3), and Case #3 by Green (2).
18	445265	P.Z.	23	WM	S-Thal	8	40	33	68	30	23	2.0	25	3.0	1.3	20	9	0	0	+++	0	—	no	Reported as Case #50 by Green (3), and as Case #2 by Green (2).
19	‡	P.	36	WM	S-Thal	10	41	31			8		20	3.4				++	0	+++	0	—	no	Repeated crises.
20	§	H.I.	27	WM	S-Thal	10	40	30					20			14	7	0	0	+++	0	—	no	Splenectomy without improvement.
21	527370	M.B.	27	CF	S-Thal	5	41	32	80	30	6		50	3.4	1.4	13	6	0	0	+++	+	—	no	Sub-arachnoid hemorrhage.
22	182730	S.S.	55	CM	S-Unclass.	10	46	38	71	31	4.6	3.2	50	3.4	1.4	17	4	+	++++	+	0	—	no	Reported as Case #49 by Green (3), and as Case #1 by Green (2).
23	464441	E.R.	25	CF	S-Unclass.	23	34	23			2.0		10	1.6		13	4	++	0	0	0	yes	no	Hemolytic anemia with pregnancy.
24	¶	A.S.		CF	S-Cong. Hem. Jau.	3							10					++	++	0	0	—	no	Complete clinical remission following splenectomy.

* Icterus index.
† Aseptic necrosis of shoulder.
‡ Patient from Sinai Hospital, Baltimore.
§ Patient of Dr. Beidleman, Pensacola, Fla.
¶ Patient of Dr. Lukens and Dr. Krevans.

TABLE II

Clinical and Hematologic Data of Nineteen Patients With Genetic Variants of Sicklemia Collected From the Medical Literature

CASE	PATIENT (AGE, RACE, SEX)	GENETIC TYPE	AGE AT ONSET OF SYMPTOMS	HEMOGLOBIN		CELL INDICES		RETICULOCYTES		TARGET CELLS %	SERUM BILIRUBIN		LEUCOCYTES × 1000/mm³		SPLEEN SIZE (0 to ++++)	CHARACTER OF CRISIS		HEMATURIA (0 to ++++)	ANEMIA WITH PREGNANCY	AVASCULAR NECROSIS OF HIPS	AUTHORS
				High %	Low %	MCV	MCHC	High %	Low %		High mg. %	Low mg. %	High	Low		Abdominal	Joint				
1	J.Y. 8 CM	S-C	2	9.6	7.0	75	30	5.8	4.6	60	.1				++-0	0	++	0	—	0	Neel, et al (14).
2	M.P. 10 CF	S-C		11	7.2	69	31	7.6	0.6	60	1.3	0.3			++		+	0	—	0	Neel, et al (14).
3	A.P. 5 CM	S-C		10.8	8.0	76	32	5.2	0.7	62	.3	.1			++		+	0	—	0	Neel, et al (14).
4	R.W. 14 CF	S-C		12.0	10.4	66	31	2.8	1.2	50	.7	.3	7.5		++-0	0	0	0	—	0	Neel, et al (14). Kaplan, et al (15).
5	T.W. 12 CM	S-C	2.5	10.8	3.5	67	32	4	1.0	70	.5		50*	9	+						Neel, et al (14). Kaplan, et al (15).
6	P.C. 5 CF	S-C	2	10.0	8.0	90	28	6.0	3.6	45	.6	.4	7.5		++-0	++	0				Neel, et al (14). Kaplan, et al (15).
7	M.S. 15 WF	S-C	5	12.0				2.9		50	.9		5.7		0	0	++	0	—		Ranney, et al (13).
8	C.S. 22 CM	S-C	?16	10.4						50			6.9		++++	0	++	++	—		Ranney, et al (13).
9	C.W. 27 CF	S-C	14	12.0	4.8				normal	50				3	+	0	+	0	yes	yes	Ranney, et al (13).
10	M.D. 13 CM	S-C	12	12.0	6.0			3.9		4				11	+	0	+	0	—	0	Ranney, et al (13).
11	E.H. 13 CM	S-C	12	10.5				2.4		10			7	4.6	+++	0	0	+	—		Ranney, et al (13).
12	36 WF	S-Thal	22	9.7		80	37	4.0		++++†				5.7	+	0	+	0	yes		Neel, et al (18).
13	34 WM	S-Thal	?24	9.7		90	28	5.2		++++			14.5		+						Neel, et al (18).
14	6 WF	S-Thal	3–4	9.0		69	31	24	9	++	1.6	1.2			+	0	0		—		Sturgeon, et al (20).
15	M.D. 41 WM	S-Thal	?6	8.5 (Ht 30)		75	28	10		+	1.2			6	+	0	++	0	—	yes	Powell, et al (21).
16	A.B 38 WF	S-Thal	?9	8.1 (Ht 32)		84	25	12		++				8.4	+-0‡	0	++	0		yes	Reich, et al (36).
17	F.B. 38 WF	S-Thal		8.3 (Ht 36)		86	23	6		++				6.7						0	Reich, et al (36).
18	I.V. 13 WM	S-Thal	1	9.2 (Ht 30)		78	27	4.9		++			14		+-0‡	0	++	0	—	yes	Reich, et al (36).
19	A.C. 33 CF	??S-C	6	6 (Ht 22)		100	27	14		+++			17.7		++	0	++	0		yes	Reich, et al (36).

* Figure not corrected for nucleated RBC's.
† (+'s) used when figures for target percentage not given.
‡ Splenectomy.

Pneumonitis and lesions suggestive of pulmonary infarcts were much less common in the variant groups than in sickle cell anemia. Clinical evidences of hepatic dysfunction associated with morphologic changes in the liver occurred in the variant cases but were mild (3). However, central nervous system manifestations, presumably caused by occlusion of small vessels by sickled erythrocytes appeared to be as frequent and as severe in the variants as in sickle cell anemia.

In the absence of hypertension and other organic cardiac disease, significant cardiac abnormalities were not encountered in patients with the variant forms of sicklemia. The enlargement of the heart and impressive murmurs so regularly found in sickle cell anemia are apparently attributable to the severe chronic anemia, since organic lesions of the heart are rarely demonstrable (25, 40). The absence of these manifestations in the variant groups is probably accounted for on the basis of the relatively mild anemia.

Patients with sickle cell anemia may develop a peculiar nephritis which may lead to uremia and death. This renal disorder was not encountered in any patient of the variant groups. Renal hematuria occurring in the absence of other demonstrable disease has been observed in some of our patients with sickle cell anemia but in a much larger percentage of the patients with sickle cell-hemoglobin C disease. Of the 27 patients with the latter disorder, gross hematuria had occurred in four. In two of our patients recurrent hematuria was a major symptom and in one had led to nephrectomy. Abel and Brown (26) reported a case in which gross hematuria was associated with sickling of the red cells, but in which the mild degree of anemia made sickle cell anemia unlikely. Goodwin, Alston and Semans (27) described the occurrence of unilateral renal hematuria in a number of patients with sicklemia. Examination of the kidneys of two of their patients revealed engorged vessels in the renal papillae and near the mucosal surface of the renal pelvis. In some areas there was slight surface erosion over the engorged vessels but no other cause of bleeding was evident. The mechanism by which hematuria is produced is obscure, and it is particularly difficult to explain the apparently greater frequency of renal bleeding in sickle cell-hemoglobin C disease.

A number of reports in the medical literature attest to a high infant and maternal mortality when pregnancy occurs in women with sickle cell anemia. In contrast, Anderson and Busby (31) in 1948 found that there had been no maternal deaths and only four infant deaths associated with sickle cell disease in the Johns Hopkins Hospital in a 20 year period. In retrospect it is now apparent that at least six of the pregnancies reported by these authors occurred in patients with variant forms of sicklemia. Furthermore, a review of the cases collected from the literature by Busby and Anderson reveals that four of the reported maternal deaths occurred in patients who may well have had sickle cell-hemoglobin C disease. Three of these patients were found at autopsy

‡ Splenectomy.

to have marked splenomegaly, and the father and infant of a fourth did not display the sickling phenomenon. In the present series of 27 cases of sickle cell-hemoglobin C disease, eight patients are known to have been pregnant on one or more occasions. Six of these had severe hemolytic crises in the last trimester of pregnancy or in the immediate post-partum period, although four had never before had symptoms referable to the blood disorder. Severe hemolytic crises occurred in pregnancy in one of the patients of our unclassified variant group, and in one of the patients with sickle cell-thalassemia described by Reich and Rosenthal (36). Since the report of Busby and Anderson, there have been three maternal deaths associated with sicklemia in the clinic population of the Johns Hopkins Hospital. It has been established that two of these patients had sickle cell-hemoglobin C disease, and the third probably had the same disorder. The morbidity and mortality during pregnancy of patients with sickle cell-hemoglobin C disease is in sharp contrast to the relatively benign pregnancies of our patients with sickle cell anemia.

The use of filter paper electrophoresis for establishing the genetic make-up of individuals with sickle cell trait and sickle cell-hemoglobin C disease gives unequivocal results. But it is important to realize that sickle cell anemia cannot always be differentiated from sickle cell-thalassemia by this technique. In one of our patients with sickle cell-thalassemia, the electrophoretic pattern was indistinguishable from that seen in sickle cell anemia, and confirmation of the diagnosis suggested by the atypical clinical course required study of other members of the family.

With the knowledge currently available concerning the clinical features of the genetic variants of sickle cell disease, it is of interest to review older literature on sickle cell disease with these disorders in mind. Certain cases previously reported appear in retrospect to have been examples of one or the other of the genetic variants. For example, one of the patients described by Bauer and Fisher (1) in their report on the "non-anemic variety" of sickle cell disease had splenomegaly and aseptic necrosis of the femoral head. It now seems likely that this patient had sickle cell-hemoglobin C disease. Virtually all of the "atypical" cases of sickle cell disease encountered in our clinic have been shown to represent genetic variants of sickle cell disease.

We wish to express our appreciation to Dr. David M. Gould of the Department of Radiology, Johns Hopkins Hospital, who performed the radiologic surveys described in this report.

BIBLIOGRAPHY

1. Bauer, J. and Fisher, L. J.: Sickle cell disease with special regard to its non-anemic variety. Arch. Surg. 1943, **47:** 553.
2. Green, T. W. and Conley, C. L.: The occurrence of symptoms of sickle cell disease in the absence of persistent anemia. Ann. Int. Med. 1951, **34:** 849.

3. Green, T. W., Conley, C. L. and Berthrong, M.: The liver in sickle cell anemia. Bull. Johns Hopkins Hosp. 1953, **92:** 99.
4. Neel, J. V.: The inheritance of sickle cell anemia. Science, 1949, **110:** 64.
5. Sherman, I. J.: Sickling phenomenon with special reference to differentiation of sickle cell anemia from sickle cell trait. Bull. Johns Hopkins Hosp. 1940, **67:** 309.
6. Harris, J. W.: Studies on the destruction of red cells. VIII. Molecular orientation in sickle cell hemoglobin solutions. Proc. Soc. Exp. Biol. & Med. 1950, **75:** 197.
7. Perutz, M. F. and Mitcheson, J. M.: State of hemoglobin in sickle cell anemia. Nature 1950, **166:** 677.
8. Pauling L., Itano, H. A., Singer, S. J. and Wells, I. C.: Sickle cell anemia, a molecular disease. Science 1949, **110:** 543.
9. Itano, H. A. and Neel, J. V.: A new inherited abnormality of human hemoglobin. Proc. Nat. Acad. Sc. 1951, **36:** 613.
10. Itano, H. A.: A third abnormal hemoglobin associated with hereditary hemolytic anemia. Proc. Nat. Acad. Sc. 1951, **37:** 775.
11. Statement concerning a system of nomenclature for the varieties of human hemoglobin. Blood 1953, **8:** 386.
12. Smith, E. W. and Conley, C. L.: Filter paper electrophoresis of human hemoglobins with special reference to the incidence and clinical significance of hemoglobin C. Bull. Johns Hopkins Hosp. 1953, **93:** 94.
13. Ranney, H. M., Larson, D. L. and McCormack, G. H.: Some clinical, biochemical and genetic observations on hemoglobin C. J. Clin. Inv. 1953, **32:** 1277.
14. Neel, J. V., Kaplan, E. and Zuelzer, W. W.: Further studies on hemoglobin C. I. A description of three additional families segregating for hemoglobin C and sickle cell hemoglobin. Blood 1953, **8:** 724.
15. Kaplan, E., Zuelzer, W. W. and Neel, J. V.: A new inherited abnormality of hemoglobin and its interaction with sickle cell hemoglobin. Blood 1952, **6:** 1240.
16. Spaet, T. H.: Identification of abnormal hemoglobins by means of paper electrophoresis. J. Lab. and Clin. Med. 1953, **41:** 6.
17. Larson, D. L. and Ranney, H. M.: Filter paper electrophoresis of human hemoglobin. J. Clin. Inv. 1953, **32:** 1070.
18. Neel, J. V., Itano, H. A. and Lawrence, J. S.: Two cases of sickle cell disease presumably due to the combination of genes for thalassemia and sickle cell hemoglobin. Blood 1953, **8:** 434.
19. Silvestroni, E. and Bianco, I.: Genetic aspects of sickle cell anemia and microdrepanocytic disease. Blood 1952, **7:** 429.
20. Sturgeon, P., Itano, H. A. and Valentine, W. N.: Chronic hemolytic anemia associated with thalassemia and sickling traits. Blood 1952, **7:** 350.
21. Powell, W. N., Rodarte, J. G. and Neel, J. V.: The occurrence in a family of Sicilian ancestry of the traits for both sickling and thalassemia. Blood 1950, **5:** 887.
22. Wasserman, C. F , Phelps, V. R. and Herzog, A. J.: Chronic hemolytic anemia in a white child due to thalassemia and sicklemia with a genealogic survey. Pediatrics 1952, **9:** 286.
23. Singer, K., Chernoff, A. I. and Singer, L.: Studies on abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation. Blood 1951, **6:** 413.
24. Lukens, D. and Krevans, J. R.: To be published.
25. Klinefelter, H. F.: The heart in sickle cell anemia. Am. J. Med. Sc. 1942, **203:** 34.
25a. Cooley, J. C., Peterson, W. L., Engel, C. E. and Jernigan, J. P.: Clinical triad of

massive splenic infarction, sicklemia trait, and high altitude flying. J. Am. Med. Assn. 1954, **154:** 111.

26. Able, M. S. and Brown, C. R.: Sickle cell disease with severe hematuria simulating renal neoplasm. J. Am. Med. Assn. 1948, **136:** 624.
27. Goodwin, W. E., Alston, E. F. and Semans, J. H.: Hematuria and sickle cell disease: unexplained, gross, unilateral, renal hematuria in negroes coincident with the sickling trait. J. Urology 1950, **63:** 78.
28. Robinson, I. B. and Sarnot, B. G.: Roentgen studies of the maxillae and mandible in sickle cell anemia. Radiology 1952, **58:** 517.
29. Duckett, H. C. and Davis, C. D.: Sickle cell anemia complicated by pregnancy. Am. J. Obst. and Gynec. 1953, **65:** 409.
30. Lash, A. F.: Sickle cell anemia in pregnancy. Am. J. Obst. & Gynec. 1934, **27:** 79.
31. Anderson, G. W. and Busby, T.: Sickle cell anemia and pregnancy. Am. J. Obst. and Gynec. 1949, **58:** 75.
32. Kaplan, E., Neel, J. V. and Zuelzer, W. W.: Further studies on hemoglobin C. II. Hematologic effect of hemoglobin C and in combination with sickle cell hemoglobin. Blood 1953, **8:** 735.
33. Spaet, T. H., Alway, R. H. and Ward, G.: Homozygous type "C" hemoglobin. Pediatrics 1953, **12:** 483.
34. Haden, R. L. and Evans, F. D.: Sickle cell anemia in the white race. Arch. Int. Med. 1937, **60:** 133.
35. Shotton, D., Crockett, C. L. and Leavell, B. S.: Splenectomy in sickle cell anemia. Report of a case and review of the literature. Blood 1951, **6:** 365.
36. Reich, R. S. and Rosenberg, N. J.: Aseptic necrosis of bone in Caucasians with chronic hemolytic anemia due to combined sickling and thalassemia traits. J. Bone and Joint Surg. 1953, **35-A:** 894.
37. Ehrenpreis, B. and Schwinger, H. N.: Sickle cell anemia. Am. J. Roentgenol. 1952, **68:** 28.
38. Hamburg, A. E.: Skeletal changes in sickle cell anemia. Report of an unusual case. J. Bone and Joint Surg. 1950, **32-A:** 893.
39. Legant, O. and Ball, R. P.: Sickle cell anemia in adults. Roentgenographic findings. Radiology 1948, **51:** 665.
40. McKusick, V. A.: The diagnosis of organic mitral stenosis in the presence of sickle cell anemia. Am. Heart J. 1953, **46:** 467.
41. Moseley, J. E. and Manly, J. B.: Aseptic necrosis of bone in sickle cell disease. Radiology, 1953, **60:** 656.

EOSINOPHILIA AND HEPATOMEGALY DUE TO *CAPILLARIA HEPATICA* INFECTION

G. F. OTTO,[1] M. BERTHRONG,[2] R. E. APPLEBY, J. C. RAWLINS AND OSCAR WILBUR

The Departments of Pathology and Pediatrics, The School of Medicine, and the Department of Parasitology, The School of Hygiene and Public Health, The Johns Hopkins University

Received for publication March 25, 1954

A review of the literature has disclosed reports of only two previous bona fide cases of human hepatic infection by the nematode *Capillaria hepatica*. The first of these (1, 2) was a 20 year old British soldier who died with symptoms suggesting a pyemia after three years service in India. At autopsy, the liver showed what was thought to be areas of suppuration but histologically these foci contained enormous number of eggs of the *Hepaticola hepatica* (*Capillaria hepatica*). The other case (3) was a 17 month old Negro child from New Orleans, who presented clinically with what was thought a severe pneumonitis and a possible meningitis. At autopsy, an enlarged liver and spleen were found with sanguinous ascites. On sectioning the liver, tiny hemorrhagic and grayish-tan foci were seen scattered throughout the tissue. Histologically, these were found to be granulomata containing eggs of *Capillaria hepatica*. The eggs were surrounded by chronic inflammatory tissue, scarring and foreign body giant cells. No adult worms were identified but one necrotic focus was found that suggested the recent dissolution of an adult parasite. Other cases have been reported in the literature in which the eggs of this nematode were found in the feces. These probably represented the passage of ingested, cooked eggs in an essentially unaltered state through the gastrointestinal tract without the actual presence of the worms or the eggs in the tissues of the patient. Indeed, in natural and in most experimental infections in animals, the eggs are not discharged from the liver into the intestinal tract. Because of the extreme rarity of the development of actual disease in man from *Capillaria hepatica*, we are reporting this case. It is also the first known example of this condition to be recognized during life.

M. W. (A-55193), a 7 year old colored female, was admitted to the Johns Hopkins Hospital on August 24, 1951, with the chief complaint of fever, shortness of breath, and epistaxis of 6 days duration. The mother and a sibling were known to have sickle cell disease. The birth and past history of the patient were uneventful until 11 months of age when she was diagnosed as having sickle cell disease with anemia. Prior to the present admission she had 3 hospitalizations for sickle cell crises which were characterized by listlessness,

[1] Present address: Research Division, Abbott Laboratories, North Chicago, Illinois.

[2] Present address: Glockner-Penrose Hospital, Colorado Springs, Colorado.

anorexia, fever, epistaxis, generalized abdominal pain, hematuria, a soft basal systolic murmur transmitted over the precordium, a protuberant abdomen, hepatosplenomegaly, leucocytosis and an anemia of approximately 6 grams of hemoglobin per 100 cc. During most of her life the child had resided in rural North Carolina except for infrequent and short visits to Baltimore. Her most recent admission had been at the age of 3 years for a sickle cell crisis. At that time there was an anemia with 6 grams of hemoglobin per 100 cc., a liver palpable 2 fingers and a spleen 3–4 fingers below the costal margin. The white blood cell count was 8250 per cmm. with 51% polymorphonuclear neutrophils 2% juvenile neutrophils, 38% lymphocytes, 8% monocytes, and 1% eosinophiles. Serum proteins were 6.7 grams per 100 cc. with an albumen of 4.4 grams and a globulin of 2.3 grams. She received transfusions and was discharged 13 days after admission. No liver function studies were done but on her second hospital admission at the age of 2½ years the cephalin flocculation had been 4 plus with a thymol turbidity of 16.6 units.

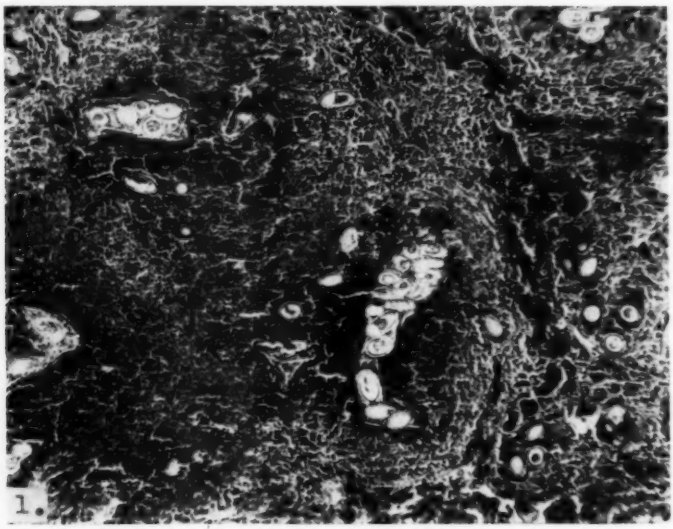
The present illness began 6 days before admission with epistaxis, high fever, anorexia, lethargy, and malaise which became more severe. She vomited clotted blood on several occasions. She developed frontal headaches, epigastric, scapular and neck pain, and dyspnea. On physical examination she was co-operative and well developed but poorly nourished and pale and was acutely, chronically, and desperately ill She preferred to lie on her side with the knees flexed. The temperature was 40.2°C., pulse 125, respirations 40, blood pressure 105 systolic and 60 diastolic, and the weight 20 kilograms. There was marked pallor of the mucosae and nailbeds. No icterus could be detected. There was moderate precordial bulging. The point of maximum impulse was in the fifth interspace on the left and the heart was enlarged about 2 to 3 centimeters both to the left and the right. The sounds were of fair quality with A2 louder than P2. A low-pitched, blowing, systolic murmur was heard at the base radiating into the great vessels of the neck. At the apex, a higher pitched, squeaking coarse murmur was transmitted to the axilla. Fluoroscopy showed increased hilar markings, a cardio-thoracic diameter ratio of about 65% and a globular configuration of the heart with apparent enlargement of all chambers. The abdomen was distended, particularly in the upper quadrants. The liver was palpable 5 centimeters below the costal margin and was tender. The spleen was palpable 2 centimeters below the costal margin and was also tender. The remainder of the physical examination was normal.

Initial laboratory examinations revealed a red blood cell count of 2.4 million per cmm., a hematocrit of 16, and a hemoglobin of 5.3 grams per 100 cc. There was pronounced anisocytosis and poikilocytosis with 10% overt sickled forms. A white blood cell count of 57,000 per cmm. was found showing 20% polymorphonuclear neutrophiles, 27% lymphocytes, and 52% eosinophiles. A

total eosinophile count was 21,000 per cmm. There was 85% sickling *in vitro* after 4 hours. The corrected sedimentation rate was 16 mm. in an hour (Wintrobe). The urine was deep amber with a specific gravity of 1.016, a pH of 5.5, a 1 plus acetone and urobilinogen detectable in a dilution of 1:40. No reducing substance, albumen, or sediment was recorded. The icteric index was 15. Blood chemistries showed a non-protein nitrogen of 22 mgm., calcium of 9.4 mgm., phosphorus of 3.2 mgm., total serum protein of 7.3 grams, with an albumen of 3.6 grams and a globulin of 3.7 grams per 100 cc. The total serum bilirubin was 2.0 mgm. per 100 cc. with a direct-reacting 1.4 mgm. per 100 cc. The CO_2 combining power was 24.2 meq. per liter and the alkaline phosphatase was 14.6 Bodansky units. The serological test for syphilis was negative. The electrocardiogram was interpreted as showing a balanced axis, and the P.R. and Q.T. intervals were at the upper limits of normal.

After admission, the heart failure and anemia were treated with digitalis, oxygen, repeated whole blood transfusions, and general supportive measures. On the seventh hospital day, an adult ascarid was spontaneously passed per rectum and ascarid eggs were found in the feces. Upon treatment with hexylresorcinol, two more ascarids were passed. Angioneurotic edema developed at this time. The patient remained febrile, anoretic and cachectic. Examination of 21 stools at intervals over the succeeding two months, by both direct saline smear and following brine concentration, failed to reveal ascarid eggs, the eggs of any other helminth, or protozoa. The eosinophilia continued with total counts of 15,000 and 30,000 eosinophiles per cmm. and one differential count of 85% eosinophiles. The liver continued to enlarge to 8 cm. below the costal margin. Liver function tests showed a thymol turbidity of 9.2 units and a cephalin flocculation of 3 plus. The total serum protein gradually rose to a high of 9.2 gm. per 100 cc. with 7.3 gm. globulin. Several paracenteses were done to relieve the increasing ascites and a thick gelatinous fluid was obtained with a protein content of about 3 gm. per 100 cc. Old tuberculin skin tests were negative as were blood cultures, a histoplasmin skin test, and various agglutinations.

On the forty-sixth hospital day a laparotomy was performed. At operation the spleen was smooth-surfaced and twice normal in size. The liver was enormous; its surface was smooth and mottled with purplish and white speckles but without gross scarring. A wedge-shaped biopsy was taken from the liver and one soft, normal appearing lymph node was removed from the lesser omental bursa. Grossly, the piece of liver (S. P. 51-5174) revealed tiny yellow foci, 1 mm. in diameter scattered evenly throughout. The lymph node was not unusual. Microscopically, there was complete disruption of all normal hepatic architecture by a parasitic infection. Necrotic foci, which were surrounded by an intense inflammatory response, were seen and were probably located in the portal areas (Figs. 1 and 2). Adult worms, which often contained eggs within



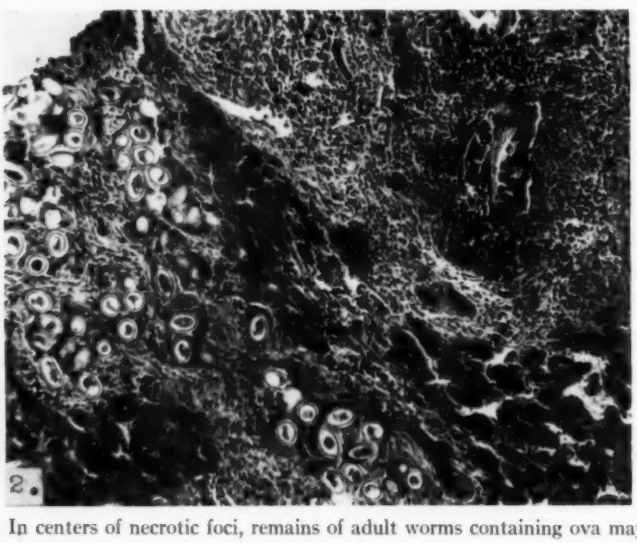


FIG. 1. In centers of necrotic foci, remains of adult worms containing ova may be seen. (1st biopsy).

FIG. 2. Fragments of adult worm surrounded by inflammatory exudate are seen in upper right while to left myriads of ova in giant cells are noted below. (1st biopsy).

their body cavities, were usually made out in the centers of these lesions (Figs. 3 and 4). These worms were sometimes well preserved and the internal organs clearly distinguished but often the worms were at least partially necrotic with preservation of only the cuticula (Figs. 1 and 2). Such worms or remnants of worms were sometimes surrounded by caseous necrotic debris (Figs. 3 and 4). The necrotic material was often brilliantly eosinophilic and, in the hemotoxylin and eosin stain, resembled so-called "fibrinoid" degeneration (Figs. 3 and 4). Multinucleated giant cells were numerous and occasionally formed syncitial masses completely enclosing the worms. Eosinophiles in profusion as well as large numbers of plasma cells and macrophages were present around such lesions. A rare caseous tuberculoid lesion without visible worms was seen, composed of caseous debris surrounded by macrophages and giant cells. In and around all lesions were enormous numbers of eggs. No remnants of adult worms were seen outside of the abscess-like areas. Scattered throughout the liver section, however, and usually in areas of considerable fibrosis, were large numbers of isolated eggs (Fig. 2). These seemed to be concentrated in what had been portal areas but the pattern of the liver was so completely lost that the location was difficult if not impossible to identify definitely. The eggs were elongated, fusiform structures with an opening at each end and with a thick hyaline capsule showing striations perpendicular to the surface. The eggs were often contained within multinucleated giant cells. Occasionally such eggs were found in the sinusoidal spaces, but even here, were enclosed in a giant cell. Development of the eggs into embryonated larval forms was not observed. The remaining hepatic cells were for the most part well preserved even though their arrangement was completely distorted. A rare eosinophilic mass, resembling a fragment of that seen in the vicinity of the necrotic worms, was seen in the Kupffer cells or in the sinusoidal lumens. A very rare Kupffer cell contained ingested red blood cells; many contained hemosiderin. No necrosis of hepatic cells was found. The lymph node showed dilatation of the sinusoids and lymphoid hyperplasia. The sinusoidal cells were often strikingly engorged with red blood cells and the sinusoids were packed with sickled forms of red cells.

The post-operative course was uneventful except for striking changes which took place in the serum calcium and the serum protein levels. The serum proteins continued to rise and reached a peak of 12.3 gm. per 100 cc. with 9.0 gm. of globulin. The calcium dropped to 5 mgm. per 100 cc. With large doses of vitamin D and calcium administration, the calcium rose to 17 mgm. per 100 cc. reaching a peak of 20.3 mgm. and remained above 14.5 mgm. throughout the hospital stay. On one occasion studies showed that most of this calcium was in the ultrafilterable fraction. It was speculated that the bizarre blood calcium changes were related to the striking alterations of serum proteins or to im-

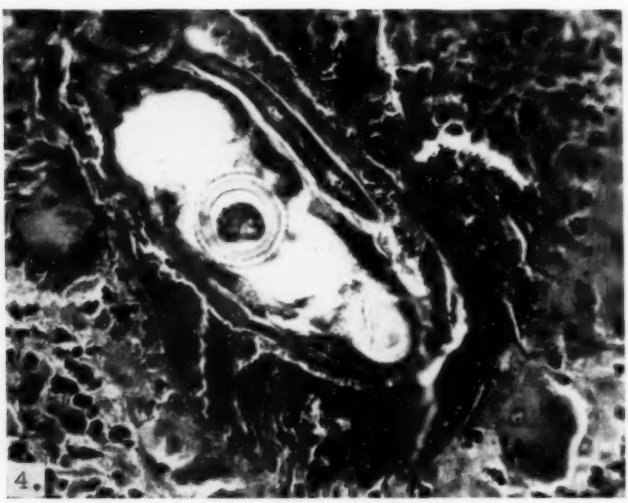


FIG. 3. Adult worm, containing an egg, is surrounded by a deeply eosinophilic amorphous material compatible with fibrinoid. Many of the surrounding leucocytes are eosinophiles. (1st biopsy).

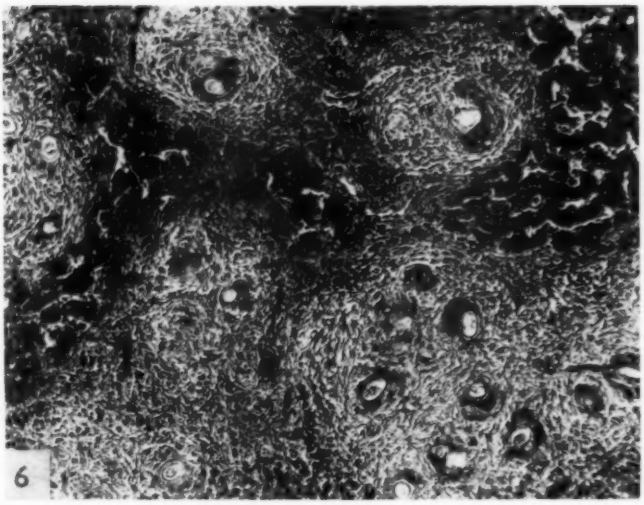
FIG. 4. A higher power view of the same field as in #3. (1st biopsy).

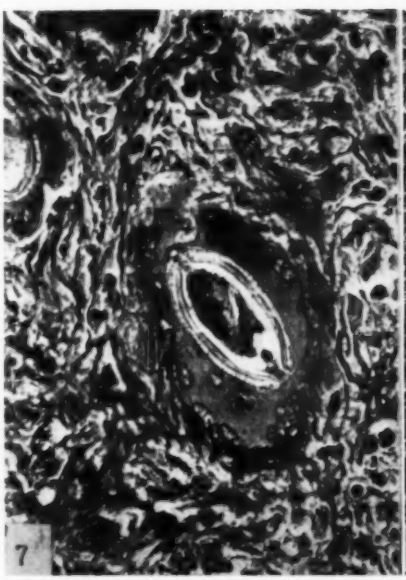
FIG. 5. Frontal and profile view of patient on 168th day of hospitalization. Lower border of liver is outlined.

paired vitamin D metabolism from the severe liver damage but a completely satisfactory explanation was never reached. The patient's well-being improved and her appetite returned. The liver continued to increase in size, however, and some attempt to destroy the worms in the liver seemed indicated. In the absence of any known specific agent, chloroquin was used because it is known to be heavily deposited in the liver and to be active against some worms. It is less hepatotoxic than other possible agents. Two four-day courses of 0.3 gm. the first day and 0.1 gm. every day for 3 days were administered during the fourth month of hospitalization (completed on the 107th day of hospitalization). The liver continued to enlarge, however, and reached 18 cm. below the costal margin by the 168th hospital day when photographs were made (Fig. 5). On the 186th hospital day a second liver bilpsy was performed.

This biopsy (S. P. 52-838) showed tiny gray foci scattered throughout the tissue. It cut with increased resistance. Sections revealed complete disruption of hepatic architecture. The gray foci were found to be broad areas of scarring containing enormous numbers of parasite eggs (Fig. 6). The eggs were fusiform with a plug at each end and a thick striated capsule. These eggs for the most part were contained within multinucleated giant cells (Fig. 7). There was little evidence of degeneration of the eggs, which usually appeared quite intact. No maturation of larvae within eggs was seen. Occasionally, however, the cytoplasm of host giant cells seemed to be extending through an opening at the end of the egg into the center. A well formed cell nucleus was seen in one such invaded egg. Fibrous tissue was abundant around these myriads of eggs with a scattering of plasma and other mononuclear cells. The eggs were most concentrated at what was thought to be portal areas but the location could not be determined with certainty. Very few eosinophiles were seen. In the sections, several well formed tubercles were present with old caseous centers, and peripheral epithelioid and giant cells (Fig. 8). No remnants of worms could be made out but eosinophiles were still present in the periphery of these tuberculoid lesions. There was considerable dilatation of portal veins, lymphatics and hepatic sinusoids. A rare Kupffer cell with erythrophagocytosis was seen. The hepatic cells were occasionally multinucleated and large but the liver cells, although markedly reduced in number, were, for the most part, normal. *Capillaria* eggs, teased out of a portion of the biopsied section of the liver, developed in tap water.

The patient's recovery from the operation was uneventful and her general condition remained good. The liver remained enlarged, however, and her hemoglobin was maintained with transfusions. No further therapy was undertaken and the patient was discharged on the 203rd hospital day. She was readmitted for follow-up 104 days later and was also examined as an outpatient 24 days later (307 and 331 days after the initial admission). On these occasions, she was found in an unchanged condition.





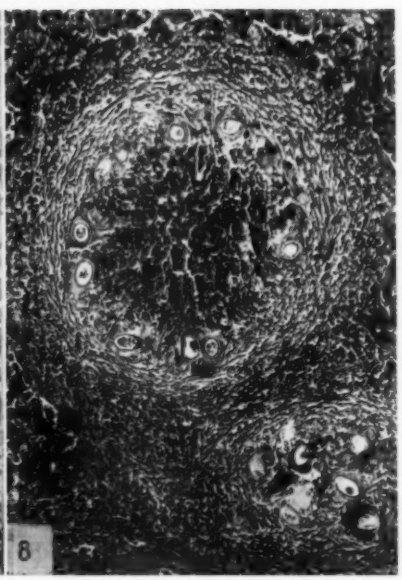


FIG. 6. Nodules of fibrosis containing the eggs of *C. hepatica* enclosed in giant cells. (2nd biopsy).

FIG. 7. The well preserved egg of *C. hepatica* enclosed in a giant cell. (2nd biopsy).

FIG. 8. One of several remaining foci of caseous necrosis surrounded by scar in which ova persist. No remnant of worm was seen in this tubercle. (2nd biopsy).

In the Spring of 1953, nearly 2 years after the onset of the acute illness thought to mark the onset of the parasitic infestation, she was admitted for weakness, nosebleeds and anorexia. On this occasion she was a chronically ill child without jaundice. There was clubbing of the fingers, a loud systolic murmur and a protuberant abdomen. The liver was slightly below the level of the umbilicus and the spleen was barely felt. There may have been fluid in the abdomen. Laboratory studies showed a hemoglobin of 4.8 grams per 100 cc., a hematocrit of 18.5, a white blood cell count of 23,900 per cmm. with 35% eosinophiles. Immediate sickling was evident. The bilirubin was 1.6 mgm. per 100 cc. with 1.0 mgm. direct. The alkaline phosphatase was 9.1 units, the total protein 4.9 gm. per 100 cc. with an albumen of 2.8 and a globulin of 2.1 gm. A cephalin flocculation was 2 plus and a thymol turbidity was 14 units. No treatment was given.

Two months after discharge, the patient was re-admitted to the hospital with an acute onset of a fever of 40.6°C. She developed convulsions shortly after admission with respiratory arrest and death occurred 5 minutes after admission.

At autopsy, (J. H. H., #24519, Dr. Wilbur), the body was well developed and nourished, weighing 26 kgm. and measuring 126 cm. in length. The abdomen was protuberant. Abdominal scars had formed keloids. There was no peripheral edema. The sclerae were questionably icteric. One thousand cc. of yellow fluid was found in the peritoneal cavity. Three-hundred cc. of clear yellow fluid was present in each pleural cavity. The thymus weighed 31 grams (normal 25 grams). The heart weighed 250 grams (normal 125 grams). There was both right and left ventricular enlargement. A markedly enlarged liver weighed 3000 grams (normal 800 grams) and measured 30 and 15 and 10 cm. The hepatic capsule showed the scars of previous biopsies. On cross sectioning, the parenchyma bulged from the cut surface. There was a pattern of interlacing strands of fibrous tissue throughout the liver. Innumerable small, yellow, caseous foci, less than 1 mm. in size, were found scattered throughout the liver. The gall bladder and bile ducts were normal. A 250 gram spleen (normal 85 grams) was very firm and dark red. Two encapsulated dark red nodules were seen in the pulp, each 1 cm. in diameter. The portal vein was normal. No esophageal varices were seen. Lymphoid tissue in the ileum and colon was prominent. Lymph nodes around the aorta, in the hilum of the liver, and in the mesentery were enlarged. The kidneys were remarkably enlarged and weighed 250 grams apiece (normal 90 grams). They were smooth with normal markings save for prominent bright red glomeruli. The adrenals weighed 11 grams together and the cut surfaces were pale brown with obvious depletion of cortical lipoid. There was a tiny focus of brown encephalomalacia in the cerebellar cortex. No other gross lesions were noted and no round worms were found in the intestine.

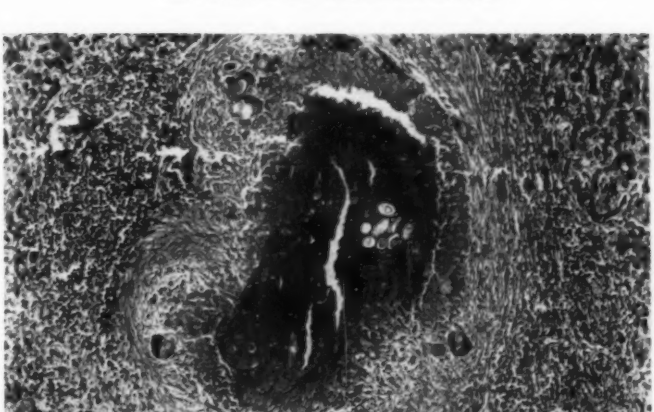
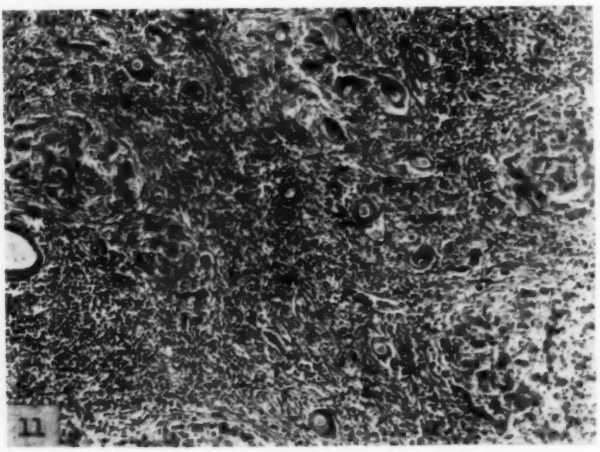


FIG. 9. Caseous focus with remnant of worm and contained eggs. Thick scar with eggs surrounds tubercle. (Autopsy).

FIG. 10. Tuberculoid focus in lung with giant cells. Probably site of disseminated parasite or eggs. (Autopsy).

Histological sections showed a liver with complete disruption of normal architecture by bands of dense fibrous tissue (Fig. 11 and 12). These scars varied in thickness, were often infiltrated by chronic inflammatory cells and eosinophiles, and usually revealed large numbers of worm eggs which were often contained within multinucleated giant cells (Fig. 11). Many of the eggs

appeared entirely normal but some showed extension of the cytoplasm and nuclei of the giant cells through the operculum into the eggs. Others were obviously undergoing dissolution. No maturation of the eggs was seen. Some of the scarring showed no trace of parasite infection (Fig. 12). Many encapsulated caseous foci were seen, often with dense accumulations of eggs in the fibrous capsules, and occasionally with shadowy remnants of dead adult worms



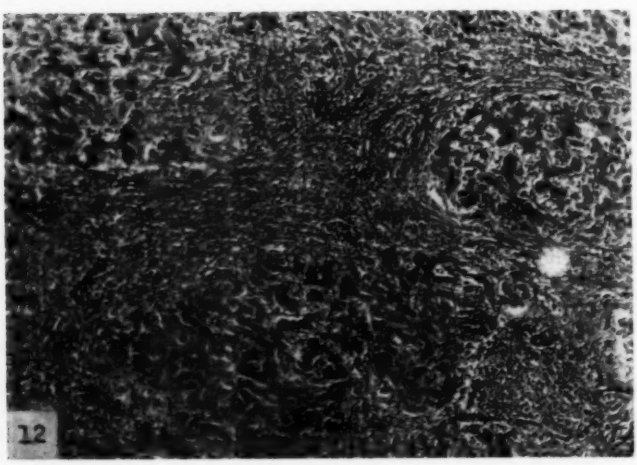


FIG. 11. Extreme scarring of liver with many eggs ingested by giant cells. (Autopsy).
FIG. 12. Scarring of liver without trace of eggs or worms. (Autopsy).

in the caseous centers (Fig. 9). Nodules of fatty and apparently regenerating liver cells were everywhere present. Bile duct proliferation was minimal. The hepatic sinusoids were engorged with red cells which were often sickled and which sometimes were found phagocytized in greatly distended Kupffer cells. Tiny foci of hepatic cell loss or recent liver cell necrosis were also seen. One of many sections of lung showed a solitary tuberculoid focus with large macrophages and giant cells. While no definite eggs were seen, hyaline and calcified bodies quite suggestive of such, were present in giant cells (Fig. 10). A pulmonary artery showed a recanalized thrombus. The spleen was massively congested with red cells, many of which were sickled. The pulp was especially packed with erythrocytes, most prominently about the Malpighian bodies. A few scars, which were heavily encrusted with hemosiderin, were found, as well as a nodule, composed of very cellular dense splenic pulp, thought to represent a splenic hamartoma. The myocardium contained foci of large mononuclear cells which lay parallel to swollen collagen fibers adjacent to small blood vessels. These were quite suggestive of Aschoff bodies. Similar lesions were seen in the left atrial endocardium. The mitral valve was normal in one section. Scarring of the pericardium was present. The renal glomeruli were engorged with blood and appeared large and cellular in spite of this. Foci of calcification in renal tubules were rarely seen as well as slight focal scarring. The esophagus showed no varices. The bone marrow was hyperplastic, with notable numbers of eosinophilic myelocytes. Several sections of cerebellum revealed very small old foci of encephalomalacia in which calcification had occurred. Many sections of striated muscle failed to reveal periarteritis nodosa.

The final anatomical diagnosis was as follows. *Capillaria hepatica* infection of liver with granulomatous lesions containing eggs and worms, cirrhosis of liver, ascites, granulomatous lesion of lung with foreign body reaction. History of sickle cell anemia with repeated crises, sickle cell lesion of the spleen with splenomegaly, marked intravascular sickling of red cells, foci of encephalomalacia, brain, cardiac hypertrophy and dilatation. Possible rheumatic myocarditis with Aschoff body formation. Renal hypertrophy with glomerular engorgement, slight focal calcification of renal tubular epithelium.

DISCUSSION

Since the *Capillaria hepatica* infection is the unique aspect of this case, it seems desirable to summarize the principal points in the recognition of the parasite and its normal life cycle. This nematode is commonly a parasite in the liver of rats. Luttermoser (4) found them in the livers of 86 per cent of over 2,500 adult rats examined post-mortem in Baltimore. The worm, however, is not confined to this host. It has been found on occasion in several other species of rodents, including mice, rabbits, and squirrels. It has also been found in ungulates, in carnivores, including the dog, and in several species of monkeys.

Infection is acquired by ingesting the embryonated eggs; the eggs hatch in the cecum where they apparently gain entrance to the portal circulation and are carried passively to the liver where the worms mature in the rat in three weeks and in the mouse in less time. Luttermoser (5) showed that there is little or no egg-laying in the host but rather the eggs are released in the liver upon the disintegration of the adult worms which in the rat usually begins within a month after infection. The eggs themselves are thought to escape from the liver only upon death of the hosts. In overwhelming experimental infections in mice, eggs are found in the digestive tract but this has not been observed in rats and is thought not to occur in natural infections of any known hosts (5). Luttermoser (6) has demonstrated that an effective method of release of these eggs under natural conditions results from cannibalism of rats. When the liver, containing the eggs, is eaten by a second rat the eggs are released by digestion and pass out with the feces of this rat. Under experimental circumstances (6), the eggs, in the one to four cell stage, require four to six weeks to become embryonated on moist soil or in aerated water. Infection is established when such embryonated eggs are ingested by a suitable host. Although eggs may be released by autolysis of the liver of a decaying rat, the process is slower and subsequent development of the eggs is uncertain, perhaps due to lack of oxygen as demonstrated by Luttermoser (6). In experimental infections, the eggs did not develop in the liver of the host, the original rat, further than the morula stage (6). Faust (7) describes the life cycle as direct without the necessity of an intermediate host. Biologically this is correct since the second rat can scarcely be called a host, but he states (apparently quoting from the work of others) that the eggs develop into fully embryonated forms in the liver within a month and the infection is transmitted directly to the animal eating such a liver. No such development was observed in the liver of the patient described in this report nor in the extensive studies by Luttermoser.

Capillaria hepatica is taxonomically in the same family as *Trichuris*, so that it is not surprising that the eggs should be similar. However, the two are readily distinguished upon careful observation. While both are barrel-shaped with a discernible plug in each end, eggs of *Capillaria* are proportionately wider than those of *Trichuris* and the plugs do not extend beyond the outer edge of the shell as with *Trichuris*. Furthermore, the shell of the *Capillaria* egg has a uniformly punctate appearance whereas there are no such markings on the shell of the *Trichuris* eggs. The eggs of *Capillaria hepatica*, as well as the liver lesions, have been discussed in the reports of Dive, Lafrenais, and MacArthur (1), Foster and Johnson (8), and McQuown (3); and the gross appearance of the liver lesions in rats is illustrated by Luttermoser (5).

The pathological finding in this 7 year old negro girl was that of extensive liver damage primarily the result of infection by *Capillaria hepatica*. While

doubtlessly the severe sickle cell disease contributed significantly to the patient's illness and possibly to her hepatic dysfunction, the histological changes in the liver showed an extremely heavy parasitization with replacement of large areas of liver cells by the worms, the eggs and the resulting necrosis, inflammation, and scar. Most of the hepatic alterations found in the two biopsies and at autopsy seemed clearly attributable to the parasites but the hepatic damage known to occur in sickle cell anemia (9) may have further aggravated the symptoms of hepatic insufficiency. In the post-mortem material, scars in the liver without eggs or worms might be attributable to the scarring occasionally found in patients dying of sickle cell disease. However, these scars were also entirely compatible with those resulting from the parasite from which all traces of eggs or worms had been lost. Erythrophagocytosis was seen in the biopsies and in the liver at autopsy as well as sickling of red cells but these were minor in comparison to the obvious results of the worms and the eggs. While cirrhosis of the liver has been found to occur in rabbits infected with this parasite (10) and while the extraordinarily heavy infection in this patient leaves little doubt that the presence of the worms and eggs caused the extensive scarring, just as Schistosoma infection is known frequently to do, it is of interest that in certain other hosts, cirrhosis has been notably absent. Foster and Johnson (8) reported that infection in the livers of monkeys and peccarys healed without cirrhosis. In mice with very heavy infection, cirrhosis occurs but in rats encapsulated hyaline and calcified scars have been described without mention of the development of a true cirrhosis (5).

Since infection by this parasite probably can occur only with the ingestion of embryonated eggs passed in the feces of an animal which had fed on an infected liver, or more rarely, of embryonated eggs from autolysis of an infected liver, the source of this patient's very heavy infestation is obscure. It would seem most likely that she acquired the infection from the eggs developing from the feces of rats. Yet that she could have received so massive a dose in this manner is certainly peculiar. Luttermoser (5) has shown that an acquired resistance to hepatic infection by repeated ingestion of eggs can be demonstrated in rats. In resistant animals, worms, once reaching the liver, may fail to mature and to reproduce. Perhaps the previously existing sickle cell disease in this child with its severe anemia resulted in a reduced resistance to the infection and to the spread and development of the adult parasite once ingestion occurred. It is still remarkable that she ingested the many thousands of eggs which would have been necessary to result in the severity of her hepatic infection. Furthermore, the ingestion of eggs must have occurred over a relatively short interval since the lesions all appeared to be of approximately the same age. Whether the resulting parasitization or consequent liver damage may have played a role in precipitating further sickle cell crises cannot be answered but

she had had many such crises previously. The continued enlargement of the liver over a period of almost a year and the persistance of the very large liver for over 2 years are also of interest. In the rat, the maximum liver damage occurs during the second month of the infection and the worms themselves usually die well within this period. Although the eggs may remain viable for as long as 8 months thereafter, there is some resolution of the process and the liver in the rats gradually becomes reduced in size. In this patient, while the adult worms also died promptly, apparently intact eggs persisted for over 2 years and an advanced cirrhosis of the liver developed. Again, the coexistance of sickle cell disease may have influenced this progression of the hepatic disease.

The biopsies in this human case, the first taken 53 days after the onset of her acute illness and the second taken 140 days after the first, indicate an interesting progression in the pathological changes in the liver. In the first biopsy, adult worms were seen to be undergoing acute necrosis or dissolution and were found to be in the centers of necrotic foci. The caseous necrosis as well as the swarms of eosinophiles suggest a hypersensitive reaction at this time. That many other adult worms had already died leaving eggs behind was clearly seen from the myriads of eggs present in the liver. Scarring, definitely present, was minimal. In the second biopsy, no adult worms could be seen and the parasitization was obviously much less acute. The liver still contained enormous numbers of intact eggs. These eggs, teased from the biopsied liver, developed normally in vitro in spite of previous therapy with chloroquin. The liver was severely scarred and evidences of vascular obstruction were prominent. The dilated intrahepatic vessels and sinusoids doubtlessly contributed to the hepatic enlargement. That such a damaged liver might further suffer from the effects of severe anemia and the vascular stasis incumbent upon the viscosity of the sickled red cells seems obvious. In the autopsy material, an occasional caseous focus still contained the shadowy remnants of dead adult worms. Hepatic scarring was even more severe. Myriads of apparently intact eggs were still seen in the scars although the inflammatory response was much reduced. The tuberculoid focus in the lung with the unidentifiable foreign material suggests that either eggs or a worm found its way there. Visceral dissemination of worms has not been observed by Luttermoser in rats but he reports that in heavy infections in mice, worms were frequently found in the peritoneal cavity and were rarely seen in the lungs and bladder (5). Nishigori, as quoted by Luttermoser (5), reported migrating but not developing worms in the lungs, kidney, and brain of infected rats. Eggs have been seen in the lungs and renal blood vessels of heavily infected mice (5). That a spread of a worm or an egg to the lung might occur in this patient with such an extensive hepatic infection is not surprising. Indeed it seems remarkable that the lungs did not show many lesions.

It is interesting that, just as in the rat, there was no evidence that the eggs were able to escape from the liver of this patient since none were found in over twenty fecal examinations over the period in excess of two months. Thus, although the diagnosis was made in the living patient, it was made only as a result of a liver biopsy and not by finding eggs in the feces. It has been noted that when *Capillaria* eggs have been found in human feces, there has been no evidence of actual infection of the tissues. Such individuals have most probably eaten the cooked livers of animals just as rats may eat the livers of other infected rats and pass the eggs in the feces. Foster and Johnson (8) have demonstrated that *Capillaria* eggs digested from cooked liver have a normal appearance but are incapable of development.

Death in this patient was the result of a remarkable combination of diseases. An acute myocarditis, which suggested either rheumatic fever or a hypersensitive reaction, was seen. Evidences of intravascular sickling were present as well as the severe cirrhosis of the liver. The brain had been previously damaged by the sickle cell disease as noted in the foci of old encephalomalacia in the cerebellum. The existance of Aschoff-like bodies raises an interesting question. Perhaps these lesions were an expression of hypersensitivity to the parasite eggs. A recent report (11) of autopsy findings in a child with visceral *Toxocara* infection included what were considered to be "allergic granulomas" as well as myocardial lesions with the general appearance of Aschoff bodies. The authors considered such lesions as manifestations of a systemic hypersensitive state. In addition periarteritis nodosa has been reported in trichina infection (12). Careful examination of all organs and of striated muscle in the present case has failed to show vascular lesions. Aschoff bodies were found within the fibers of the left atrial endocardium in the present case, an unusual location for the lesions of hypersensitive reaction to drugs or foreign proteins. It is certainly possible that this patient had acute rheumatic fever in addition to sickle cell disease and parasitic infection of the liver but it seems most likely that the lesions were a manifestation of hypersensitivity to the parasitic infection.

SUMMARY

A case of massive hepatic infection by *Capillaria hepatica* has been described. The liver was severely damaged and, two years after infection, showed a diffuse cirrhosis with persistance of large numbers of intact eggs. The patient had concomitant sickle cell disease and, at autopsy, also showed the lesions of acute myocarditis suggesting either rheumatic fever of hypersensitivity to the parasite. The possible interrelation of these diseases has been briefly discussed as well as the peculiar life cycle of the parasite. The source of her infection is not known but it is assumed that it came from rats, known to be frequently in-

fected by this parasite. Chloroquin therapy was no avail and eggs obtained from the liver developed normally in vitro after this drug had been administered.

REFERENCES CITED

1. Dive, G. H., Lafronais, H. M. and MacArthur, W. P.: A case of deposition of eggs of *Hepaticola hepatica* in the human liver. With a note on the identity of the eggs. Roy. Army Corps, 1924, **43:** 1–4.
2. MacArthur, W. P.: A case of infestation of human liver with *Hepaticola hepatica* (Bancroft, 1893) Hall 1916; with sections from the liver. Proc. Roy. Soc. Med. (Sect. Trop. Dis. and Parasitol.), 1924, **17:** 83–84.
3. McQuown, A. L.: Capillaria hepatica: Report of genuine and spurious cases. Am. J. Trop. Med., 1950, **30:** 761–767.
4. Luttermoser, G. W.: A helminthological survey of Baltimore house rats (Rattus norwegicus). Am. J. Hyg., 1936, **24:** 350–360.
5. Luttermoser, G. W.: An experimental study of *Capillaria hepatica* in the rat and mouse. Am. J. Hyg., 1938, **27:** 321–340.
6. Luttermoser, G. W.: Factors influencing the development and viability of the eggs of *Capillaria hepatica*. Am. J. Hyg., 1938, **27:** 275–289.
7. Faust, E. C. *Human Helminthology*, 3rd Edition, 1949, Lea and Febiger.
8. Foster, A. D. and Johnson, C. M.: An explanation for the occurrence of *Capillaria hepatica* ova in human feces suggested by the finding of three new hosts used as food. Tr. Roy. Soc. Trop. Med. and Hyg., 1939, **32:** 639–644.
9. Green, T. W., Conley, C. L. and Berthrong, M.: The liver in sickle cell disease. Bull. Johns Hopkins Hosp., 1953, **92:** 99.
10. Suda, K.: On liver cirrhosis in the rabbit caused by *Hepaticola hepatica*. J. Med. Assn. Aichi., 1928, **35:** No. 1.
11. Brill, R., Churg, J. and Beaver, P. C.: Allergic granulomatosis associated with visceral larva migrans. Am. J. Clin. Path., 1953, **23:** 1208.
12. Reimann, H. A., Price, A. H. and Herbert, P. A.: Trichinosis and periarteritis nodosa. J. Am. Med. Assn., 1943, **122:** 274.

THE EVOLUTION OF PULMONARY TUBERCULOSIS AND ITS BEHAVIOR UNDER TREATMENT[1]

J. BURNS AMBERSON

Professor of Medicine, Columbia University College of Physicians and Surgeons. Visiting Physician-in-Charge, Chest Service, Bellevue Hospital, New York

Received for publication April 6, 1954

The current changes in the treatment of tuberculosis are much more profound and promising of good than any of the past. They are to be attributed to progressive improvement of diagnostic methods, the discovery of specific antibacterial drugs, the widening scope of thoracic surgery, and a clearer understanding of the pathogenesis of the disease. The results already achieved have engendered high hopes among patients and physicians and a degree of optimism which sometimes exceeds reason. There is indeed some justification of a change from the strong note of fatalism which during past generations pervaded the thinking on therapy. In those times little was known of the early stages of tuberculosis, and the great majority of cases were advanced at the time of the first diagnosis. Consequently, the prognosis usually was considered to be grim and there were widely accepted axioms that the only reasonable attitude for the patient was one of acquiescence and willingness to go away—to the sea, to the desert, or to some magic mountain, where perhaps Nature would be kind and heal him. Once tuberculous, always tuberculous! One might learn to live with his disease, perhaps usefully if not happily, but with the expectation that eventually he would succumb to it. Today, when there is an opportunity to make the diagnosis early and to apply treatment promptly, the prospect of recovery is great and the hazard of relapse and prolonged invalidism is less than ever before this era. While the benefit is more certain, the techniques of treatment have become more intricate and the need of fine judgment in using them more pressing; some of these techniques are still tentative, and improvements are to be expected as experience accumulates.

While the morphologic pathology of tuberculosis is very familiar and sometimes said to be uninteresting, the increasing opportunities of treatment have stimulated an important effort to identify more clearly the nature and sequence of the mechanisms involved in pathogenesis and to establish correlations which have a meaning in clinical terms. The roentgenogram and more exact bacteriologic techniques have been valuable instrumentalities in this work. In the previous lecture reference was made to the similarities and dissimilarities of

[1] Lecture II of the nineteenth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine. Delivered at The Johns Hopkins Hospital April 30, 1953.

necrosing lesions of the lung and the features which set off tuberculosis as a unique problem. In principle, tuberculosis is treated much the same as non-tuberculous necrosing inflammations, at least during the early phase when specific drugs and measures to promote resistance of the body are employed to suppress bacterial activity. Beyond this point, however, the path diverges because of the long survival of the tubercle bacillus in the tissues, the peculiar slowness of softening and sloughing of the necrotic tuberculous lesion, the tendency of this to be sequestered and retained in the lung as an ever threatening focus and the transmission of virulent infection to other parts when sloughing does occur. Tuberculosis is at once a self-healing and a self-perpetuating disease and we are lost unless we learn something of the circumstances.

It is familiar that tuberculosis manifests itself most often in the lungs and that this form is by far the chief cause of progressive disease, disability and fatality. It is now commonplace in this country to find groups of adolescent youths of whom only 10 or 15 per cent react to the tuberculin test, a great change from a generation ago when the rate was frequently 60 to 80 per cent. This is interpreted to reflect a postponement of primary infection into later years of life. As a consequence, fatalities from acute generalized miliary tuberculosis and meningitis, which are most frequent in infancy and early childhood, have declined much more rapidly than those from the pulmonary form which characteristically becomes most prevalent during and after the age of adolescence. Now it is assumed that, in young people at least, most pulmonary disease represents an immediate or somewhat delayed progression from the primary lesion; the frequency of severe extensions into the tracheobronchial lymph nodes and through the blood stream is relatively less than in infancy and the center of the trouble, therefore, is most often found in the parenchymal lesion. At its start, this may be limited to a single segment of one lobe of one lung, according to Medlar (1), and it has all the features of tuberculous lobular pneumonia. The lesion is usually first identified by x-ray examination because of the small soft-looking mottled cloudy shadow, several centimeters or less in diameter. Comparisons with the actual pathology usually reveal that the involvement is somewhat greater than suspected from the x-ray shadow and that it has already undergone some necrosis; frequently there are satellite or secondary lesions in the immediate vicinity. In other words, the x-ray shadow usually portrays a conglomeration of small lesions within a limited area of the lung. This finding obviously implies that there is an earlier phase of evolution during which the focus is so small that it cannot be readily identified even by the roentgenogram. Most people who react to tuberculin must have had this early, minute lobular pneumonia which healed without further progressing. A size sufficient to permit identification indicates therefore that local progression has occurred and that the defenses have not been adequate to cope completely with the infection during its incipiency. The occurrence of satellite lesions is

explained most often by local bronchial spread; this is inferred from their frequent proximity to a focus which is sloughing its contents through communicating bronchioles. Here then we have in miniature a picture of the fundamental mechanisms of progressive pulmonary disease. The prerequisites are necrosis, liquefaction and sloughing, the inhalation of discharged pus through the bronchi into healthy alveoli, and the capacity of the bacillus easily to initiate lesions in these new sites.

The clinical correlations in this phase are important. Tuberculous toxemia depends greatly on the extent and acuteness of the inflammation and, in comparison with that caused by many other pyogenic infections, is relatively mild. Consequently, patients with early pulmonary disease usually consider themselves healthy. Some may experience slight fatigue and loss of weight. A few report pain referable to local pleurisy, and still fewer have early tuberculous pleural effusions, usually with fever. An interesting feature is the lack of cough, which does not develop until later when there is considerable discharge through the bronchi from a widely sloughing lesion. Earlier, the discharge is scanty and does not concern the patient; the material is swallowed and he denies expectoration. However, repeated cultures of specimens obtained in the morning or of the fasting stomach contents often reveal tubercle bacilli. Abnormal physical signs are notoriously few though in a minority of cases local rales may be heard. Later, as liquefaction proceeds, rales are more often elicited on auscultation.

The later evolution of the pulmonary lesion does not differ greatly in kind though it frequently does in rate and severity; the wide variations partly reflect great differences in the resistance of patients and its changing levels in the same patient. The infection, having been firmly intrenched, the later issue is a matter of balance of forces between the invader and the defenses of the host.

There is no precise way of measuring native resistance or specific acquired immunity, and the impressions gained from the usual observations of the patient's physique and general health are not very dependable. In cases of disease of recent origin the response to treatment with rest in bed is the best available criterion. The observations in the first weeks and months should be frequent and should include roentgenograms every week or two, recording of sputum production and repeated searches for tubercle bacilli. These are fairly good indices of the behavior of the lesion and often reveal early changes which may be interpreted in terms of resistance and prognosis.

When the infection is not immediately checked these early lesions usually run a slow and indolent course, but the variations are numerous and some give rise to severe and rapidly progressive disease which may be traceable to early liquefaction of the necrotic mass. Sloughing at this time may be detected by increasing purulent sputum, increasing rales and roentgenographic evidence of excavation; in some cases it is associated with or followed by acute symptomatic exacerbations and pneumonic extensions. The acute pneumonia most

often is in the vicinity of the original lesion but soon may become more widespread and bilateral. This depends somewhat on the amount of pus being discharged from the cavity and also on its physical character and bacillary content. The more liquid it is, the more easily may it be drawn by inhalation through the minute bronchioles into the alveoli; and the more heavily charged it is with organisms, the more intense will be the pneumonic reaction. The importance of the physical composition of the material is emphasized by a contrasting situation seen at times in chronic cases. Some of these patients who have fibroid pulmonary cavities which constantly discharge tubercle bacilli tolerate the disease for twenty or thirty years with little or no evidence of spread into healthy parts of the lungs. The safeguard seems to be in the thick nummular mucoid or mucopurulent character of the sputum, forming a coherent viscid semifluid mass which cannot be easily inhaled through the finer air passages but is readily and completely expectorated. The situation may change abruptly, and acute pneumonic spread may occur during hemoptyses; the fluidity of the blood is such that infection is now easily carried into the alveoli.

The more common type of progression from the early limited lesion is small, slow, often intermittent but sometimes continuous. There may be multiple areas of lobular pneumonia, several centimeters in diameter and confined mainly in the vicinity of the lesion of origin, or wider distributions with small infiltrates cropping up in distant parts of the same lobe or in other lobes of the same or opposite lung. Whatever the size of the secondary lesions, they possess essentially the same potentialities as the original. At any of the sites necrosis may occur and this again varies greatly in its rate and intensity; finally, local sloughing and cavities may appear. Here again one is sometimes struck by the difference in the evolution of secondary bronchogenic lesions in old chronic cases, the source of the spread being a partly fibroid cavity; these secondary lesions as a rule do not go on to excavation as rapidly or extensively as those originating in an early case. The virulence of the organisms has not been shown to differ. The old cavity may be casting off fewer bacilli and the concentration of dose at the new site of implantation may be less. Another factor is the probability that the patient with old chronic disease, sometimes called "the good chronic," has a high level of resistance which may determine the more effective reaction to the new implantations while mechanical factors such as surrounding dense fibrosis and pleural adhesions prevent the contraction and closure of the cavity.

In some respects, the crucial period of tuberculosis is during its early phases. It is at this time above all others that resistance to the infection may increase to suppress it completely and lastingly. In the case following recent primary infection one has the vague impression that specific acquired immunity rises slowly during a year or so, but there is no exact information. There is a significant correlation between the response to treatment during the first two years

TABLE I*

Results of Treatment of 90 Cases of Minimal Tuberculosis Occurring in Student Nurses
(Period of Observation—Five to Twenty Years)

I. Disease considered to be clinically stable after two years of treatment (9 with pneumothorax now re-expanded)		65
Relapses with subsequent recovery		7
Status in 1952		
Dead	3	
Due to tuberculosis	0	
Due to anesthetic related to surgery for tuberculosis	1	
Suicide	2	
Under treatment	0	
Living and well	62	
		65
II. Disease considered to be clinically unstable at the end of two years of treatment		25
Relapses or chronically active clinical course		17
Status in 1952		
Dead	4	
Due to tuberculosis	3	
Due to anesthetic related to surgery for tuberculosis	1	
Under treatment or limited in activity	13	
Living and well	8	
		25

* Prepared by Dr. Julia M. Jones.

and the later prognosis (Table I). If the "minimal" lesion remains within its bounds or diminishes during this period, the rate of relapse afterwards is very low; on the contrary, in our experience, the lesions which were still unstable at the end of two years frequently remained so, and the rate of relapse was high; in a few cases the disease went on to a fatal ending. The probability is that in many cases the eventual outcome is foreshadowed within the first few months of origin.

Taking another view from these observations, it is apparent that chronicity of the disease may be established within a year or two. At this point, even if resistance seems to have improved and symptoms are few and mild, the future outcome depends greatly on the morphology and composition of the remaining lesions. Those which are small and well organized and encapsulated by fibrous tissue are likely to remain permanently arrested. Others which are larger, i.e., two or three centimeters or more in diameter, and have necrotic centers tend more often later to undergo liquefaction and sloughing. Cavities which may have become stationary, continue nevertheless to discharge tubercle bacilli, and progression of the disease sooner or later is very frequent. In studying encapsulated caseous lesions, even those of small size (1 cm. or less in diameter) Medlar has demonstrated that a communication with the bronchioles almost always persists, providing a permanent exit through which infection may

escape. So long as the necrotic matter remains inspissated and semisolid its physical state prevents its passing the tiny aperture. When converted to pus, however, it seeps out freely, carrying bacilli with it. The liquefaction conceivably may be minimal or intermittent, thus accounting in some cases for occasional positive cultures of the sputum or gastric contents of patients with apparently "inactive" disease. Such positive findings, however, disclose a threat of more serious happenings and, especially in young people, are now regarded with more gravity than in past decades.

Now that a number of specific chemotherapeutic agents, including streptomycin, isoniazid, para-aminosalicylic acid and viomycin, are available their use in clinical practice so modifies the course of pulmonary tuberculosis that new questions arise and many familiar phenomena can be viewed from new angles. At first, when streptomycin alone was used, an important limitation was the predominance after several months of treatment of drug resistant strains of the tubercle bacillus which overran the field of disease and often continued the destructive process. The fortunate discovery that the simultaneous administration of two or more different drugs of this group helps to inhibit the proliferation of resistant strains during many months opened the way for the prolonged treatment which often is so necessary to be really effective. This, when indicated in preparation for surgery, also affords frequent opportunities for the study of freshly excised specimens of diseased tissue. In the Chest Service of Bellevue Hospital, we have enjoyed the great advantages of the preparation and interpretation of these at the start by E. M. Medlar and later by Marvin Kuschner. It has thus been possible to identify clinical correlations closely.

The effect of chemotherapy on pulmonary lesions has not been found to differ greatly from that brought about by natural resistance to the infection except in degree and rate. Whether it be the rest "cure" or chemotherapy the first favorable response is a subsidence of active inflammation. This is reflected in the alleviation and disappearance of general symptoms of toxemia, the halting of the extension of lesions demonstrated by x-ray, and a diminution of exudation as indicated by the decreasing amount and changing composition of the sputum. The rate of these changes varies greatly under any conditions but is generally more rapid under chemotherapy. In the case of highly acute caseous pneumonia, for instance, six or eight weeks or even more may pass before the severe inflammation comes to a halt; but it is recalled that, under rest treatment alone, most of these lesions progressed without interruption. As might be expected the milder cases usually respond more promptly.

An unclear point is the effect of chemotherapy in stopping the process of necrosis in existing lesions. According to clinical observations the best assurance of this is in the demonstration of resolution. While necrosis may take place in any part of an exudative lesion, the process is prevented in areas in which

resolution intervenes and continues to completion. However, while resolution of exudate about the periphery of a lesion may occur, the necrotic center may continue to undergo liquefaction and excavation. The same phenomenon is seen in cases not treated with drugs but appears to be more gradual, less striking and less frequent; in any event excavation occurs most conspicuously in acute cases in which extensive caseation has taken place presumably before the start of treatment. In other cases, usually more mild, chemotherapy seems to arrest the process of sloughing and the caseous matter may become inspissated. Since the semisolid necrotic mass is capable of sloughing later, after months or years of quiescence, the theoretical question arises whether it might be better to allow the abscess to evacuate itself early, leaving a cavity which under chemotherapy, might be capable of more durable healing somewhat comparable to that of a nontuberculous abscess. The alternatives deserve thought and would be of great practical importance if we had a drug with sure bactericidal powers.

Once active inflammation is halted with the aid of chemotherapy and resolution is initiated it usually continues to its maximum during weeks or months. As in the natural course of the disease, it is stopped at the border of the caseous center. In time, therefore, the unchanging character of dense, sometimes rounded lesions is taken as a measure of the volume of necrotic residues; its validity for such interpretation has been demonstrated by the study of resected specimens. At this point and so long as effective chemotherapy is continued sloughing seldom occurs. It is a fortunate situation since such lesions can usually be held under control if more time is required for other purposes. More will be said about this later.

After its necrotic contents have been evacuated a pulmonary cavity under chemotherapy tends to shrink more rapidly than it does without such treatment. Shrinkage may occur early and may be favored by the resolution of edematous inflammatory lesions of the mucosa of communicating bronchi which usually respond very well. The abatement of this obstruction improves ventilation, releases partly trapped air which may have distended the cavity and facilitates the drainage of purulent exudate; at the same time the resolution of lesions about the wall of the cavity may allow freer movement of the elastic parenchyma as the cavity tends to collapse. A striking feature after some weeks or months of chemotherapy is the frequent disappearance of sputum and the failure any longer to recover tubercle bacilli in cultures of specimens while the cavity remains, a phenomenon which otherwise is not observed. Under rest treatment without drugs these outward signs would be taken as reliable evidence of the closure of the cavity. This peculiar effect of chemotherapy has raised the question whether cavities while still "open" may nevertheless undergo substantial or complete healing. While pathologically the walls of some of these cavities have been shown to consist largely of "clean" fibrous tissue

and Auerbach (2) has emphasized the extension of bronchial epithelium over small parts of their surface, it is observed that elements of tuberculosis persist in most or all of them; therefore, the supposition of complete "open healing" is not supported. The apparent explanation of the absence of sputum containing bacilli is the strong and rapid bacteriostatic effect of the chemotherapy and the consequent cessation of exudation from the interior of the cavity. This is a highly effective preventive of progressive disease due to the common process of bronchial dissemination since the usual source of the infectious discharges is dried up. Compared with conditions when a patient is active and working, the discharge from cavities often diminishes greatly under the rest "cure" alone but, as stated, it does not cease unless and until the cavity closes; this fact often explains relapses during the course of otherwise smooth and steady recovery. The drying effect of chemotherapy often does much to avert these spreads of infection and to confine the bacillus until the lesion "closes" or can be eliminated surgically. Because of the abatement of the destructive process hemorrhages from cavities during chemotherapy are also relatively infrequent; when they do occur fresh pneumonic lesions may be set up by the transported infection but these seem to resolve promptly.

Another phenomenon is the frequent relatively rapid disappearance of auscultatory rales from many diseased areas under the influence of specific drugs; this too is best explained by the subsidence of exudation. It often occurs before there is time for fibrosis to develop and, therefore, should not be interpreted too soon as a sign of dependable healing. This observation throws some light on the failure of rales to clear away so often and so strikingly during recovery without chemotherapy and suggests that their persistence may indicate mild local activity of the infection after all other perceptible manifestations have subsided. This does not ignore the possibility that in some cases which have remained clinically inactive, perhaps for decades, rales may be due to other changes such as fibrotic distortion of the bronchioles and stagnation of secretions.

The correlation of the histological features of resected lesions with the clinical background of the case is the best means of studying the rate of fibrosis. So far as our observations have gone, it appears that this may develop extensively in lesions of recent origin during six to twelve months of rest treatment with chemotherapy. It is doubtful whether fibrosis is accelerated beyond the "normal" rate. Since it is often retarded by stubbornly active infection, the important effect of the drugs in this respect may well be the elimination of this delaying action by their strong and sustained antibacterial action.

The change of the growth characteristics of tubercle bacilli obtained from solid and semisolid necrotic lesions which have been treated with drugs requires further study by bacteriologists. Dubos (3) and others have expressed skepti-

cism that all these organisms, which are morphologically intact but sometimes fail to grow in artificial culture media and to infect guinea pigs, are dead. Relapses have been observed in patients after long periods of apparently effective chemotherapy. In clinical practice, therefore, it cannot be assumed that all, if any, of the lesions are sterilized. When they do well after the discontinuance of chemotherapy, it seems more reasonable to give credit to the adequacy of the patient's resistance and healing powers. The practical importance of this supposition is evident since it implies the necessity of regulating the activities of patients in order to guard against relapse.

A question of considerable importance is whether a given status of healing under rest treatment alone is as favorable and durable as that which is achieved with the addition of chemotherapy. Under the latter condition the evidence is convincing that the healing processes are accelerated and there is a strong presumption that, in many lesions, the vital properties of tubercle bacilli are changed, at least temporarily, and at a relatively rapid rate. Little is known, however, about the state of vital resistance. If at the onset of the disease resistance is low, it may rise possibly very slowly. In some cases in which chemotherapy is terminated at the end of six or eight weeks the early and favorable response has been followed by serious and prompt relapse; in others the course toward recovery has continued without interruption. This, of course leads to the suspicion that the level of resistance is not the same. On the other hand, such differences do not appear so frequently when chemotherapy is continued for a year or more before stopping and it is a question whether, during this prolonged period of time, the artificial suppression of the infection has not only held the disease in abeyance but has also favored improvement of the initially low resistance. The answer will require much more time and will be related to the frequency and time of relapses. Since the state of resistance is vitally important, the need for an objective measure of it is emphasized anew. During the rest cure, an estimate may be obtained by observing the patient's reaction to gradually increasing physical activity, but under chemotherapy it is a problem to decide whether the satisfactory tolerance of such a test is due to the artifice of drugs or to bodily resistance. Consequently, there is a growing practice of continuing chemotherapy for a year or more after the disease appears to be inactive. This is wise in acutely grave situations such as generalized miliary disease or meningitis but is probably unnecessary in some of the pulmonary cases. It may be disadvantageous because of the development of bacterial drug resistance. Since there are no clear-cut criteria for discontinuance, the usefulness of approximate clinical indications must be recognized. Thus far it has appeared that relapses are most frequent, even after a year or two, in cases of apparently quiescent caseous pneumonic disease and in those with chronic cavities. When the disease has been reduced to a

few residual partly encapsulated necrotic foci, the size of these is significant. In such situations, therefore, a choice frequently has to be made between continuing a regimen of chemotherapy or resorting to surgery for the collapse or resection of the lesions. In the case of a small lesion which appears to have undergone satisfactory healing, a known background of chronicity prior to treatment may justify stopping chemotherapy after three to six months on the assumption that the mildness of the disease reflected a good level of resistance. The margin of safety is usually great and proper observation will promptly detect a possible reactivation of the lesion, and the original regimen of chemotherapy may be resumed or another substituted.

The widening of the scope of surgery by chemotherapy is truly a marvel, the most striking feature being the degree of safety with which diseased pulmonary tissue may be removed. Two relevant matters are the timing of surgery and the necessity of treatment afterwards. On both scores there is pressure to hurry in order to save the patient's time and earning power but, within reasonable limits, this may be minor compared with the value of lasting recovery. While some lesions may seem well localized and fit for resection after a few weeks of chemotherapy, his resistance against the infection may still be poor and it may be better to allow more time for improvement. Except perhaps in early "minimal" lesions, it must be assumed that the infection has spread to other parts of the lungs and often elsewhere; these secondary foci may be small and capable of healing permanently but their potentialities should not be ignored. For these and other reasons also, careful judgment should be exercised in determining the period of treatment postoperatively. Some of our patients, known to have very limited chronic disease in a rather steady though unsatisfactory state for two years or more, have returned to part-time work with apparent safety after three to six months of convalescence and chemotherapy. However, those with acute widespread disease which has been sufficiently controlled to warrant surgery are usually advised to continue on a regimen of rest and chemotherapy for six months to a year or more before resuming their usual activities; this of course depends on the extent as well as the severity of the disease before treatment and the nature of the lesions remaining after surgery.

To summarize the purposes of this lecture, some of the identifiable factors which play their parts in the course of pulmonary tuberculosis have been discussed. Their modification by chemotherapy is often significant, and explanations are suggested. Since the successful treatment of the disease requires careful judgment of the individual case and its various changes, these are interpreted in clinical terms which may serve as practical guides. The problems remaining for solution are numerous and worthy of the efforts of those who are interested and competent.

REFERENCES

1. Medlar, E. M.: The pathogenesis of minimal tuberculosis. Am. Rev. Tuberc., 1948, **58:** 583.
2. Auerbach, O., Katz, H. L. and Small, M. J.: The effect of streptomycin therapy on the bronchocavitary junction and its relation to cavity healing. Am. Rev. Tuberc. 1953, **67:** 173.
3. Dubos, R. J.: Discussion of papers dealing with the bacteriology of resected pulmonary lesions. Trans. Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration: Army: Navy, 1953.

ABSTRACTS OF PAPERS PRESENTED BEFORE THE JOHNS HOPKINS MEDICAL SOCIETY IN ASSOCIATION WITH THE ALPHA OMEGA ALPHA FRATERNITY

April 12, 1954

ELECTRON MICROSCOPY OF DEVELOPING SKELETAL MUSCLE

James L. Frost

As a control for future work with virus infections, the structure of the striated muscle of 4-day mice was studied with the electron microscope. This study shows that this developing muscle exhibits the basic structural details characteristic of adult muscle.

The muscles used were those of the gastrocnemius-soleus group. The tissue was fixed in 1 per cent osmium tetroxide, and dehydrated and embedded according to the standard procedure for electron microscopy.

The developing muscle fiber at this stage is a bi-nucleate or multi-nucleate cell. Myofibrils possessing cross-bands are present. Mitochondria are found between the myofibrils in close apposition to them and between the myofibrils and the cell membrane. Sarcoplasm fills the remaining space within the cell. The spaces seen between cell membranes may be connective tissue spaces, or may be due to separation during polymerization of the embedding media.

Several differences between the developing and the adult muscle are evident, primarily with respect to the myofibrils. There is a scarcity of myofibrils, perhaps because of the early distribution of the myofibrils at the periphery of the cell. A section at the surface of the cell shows many more myofibrils than one through the middle of the cell. The tissue studied is beyond that stage of development because the nucleus, which in early stages has a central position, is now at the periphery next to the cell membrane, and some myofibrils are in the center of the cell. The nuclear-myofibril spatial relationship is intimate. Myofibrils were seen in a position directly against the nuclear membrane. On either side of the nucleus, the myofibril bends and comes to lie close to the cell membrane. A small number of myofibrils is present, in comparison to adult muscle.

The size of the myofibrils varies. Some are quite small, others are considerably larger. Those of adult muscle are of fairly uniform size.

The myofibrils of the developing muscle exhibit a "branching" structure. This "branching" is characteristic of all the 4-day muscle seen in the electron microscope. This is not seen in the adult tissue, in which each myofibril is separate.

A myofibril is composed of many longitudinal filaments. These have been called myofilaments. They are separate entities, closely and regularly packed within the myofibril. Sections cut at right angles to the axis of these filaments show their arrangement in rows within the myofibril.

Previous studies with the light microscope have shown that the number of myofibrils increases as development progresses and that the size of individual myofibrils increases. Light microscopy has also shown that the initial myofibrils are formed by deposition from the sarcoplasm. The "branching" of the myofibrils is involved in the development of the myofibrils. This study has not indicated whether the increase in number is due to splitting of the existing myofibrils or to the continued deposition of new myofilaments which combine to form new myofibrils. It also does not indicate whether the increase in size is due to a continued deposition of the individual myofilaments next to myofibrils already present, or to the combining of newly deposited myofilaments with one another. The use of serial sec-

tions and the study of developmental stages before and after this 4-day stage may clarify this point.

All of the cross-bands characteristic of the adult may be present. In some of the specimens, certain of the bands are not well defined, or may be absent. Within a fiber, the H and M bands may be present in some myofibrils and missing in others. In some fibers only the A, I, and Z bands were seen; the H, M, and N bands were absent. Absence of certain of the bands may indicate that the myofibrils are not fully developed. Their appearance may be an indication of the developmental stage of a myofibril or of a fiber.

A fine cross-striation existing throughout the myofibrils was seen in the electron microscope. It is present in both the A and I bands. This striation may be due to the plane of sectioning not being exactly parallel to the axis of the myofibrils, resulting in successive layers of the myofilaments being cut in such a way as to produce alternating dark and light lines. It might also be due to small enlargements of the myofilaments which Bennett and Porter have reported to have a 225 angstrom periodicity. The periodicity range of these striations, 150–250 angstroms, includes the figure they give.

In summary it may be said that developing muscle, as seen in the electron microscope, possesses the basic structural details which light and electron microscopy have shown for adult muscle.

Characteristic of this developing muscle is (1) a small number of myofibrils within a cell, (2) variation in the size of the myofibrils, (3) "branching" of individual myofibrils, and (4) occasional absence of certain of the cross-bands. These characteristics are in contrast to the structure of adult muscle and seem indicative of developmental stages.

EFFECTS OF CORTISONE ON THE MORPHOLOGY OF THE MOUSE ADRENAL WITH SPECIAL REFERENCE TO CHANGES IN THE X-ZONE

James C. Allen*

The adrenal cortex of the immature mouse bears a transitory histological zone which is related to the age and sex of the individual mouse. Howard's original description pictured this transitory zone, or "X-zone", as being composed of small, densely staining cells lying between the "adult" or "permanent" cortex and the medulla. The origin of the zone was discussed and a description of its development, duration and degeneration was given, comparing the two sexes in these respects. It was pointed out that in both sexes of the mouse the onset of X-zone degeneration is roughly coincident with the development of sexual maturity. The effect of pregnancy to cause rapid involution, and of castration to prevent degeneration in the prepuberal male mouse was summarized. The development of a "secondary X-zone" similar in most respects to the primary zone following suppression of lactation in the post-parturient female and following castration of the adult male mouse was reviewed. A comparison of the mouse X-zone to the "fetal reticularis" of the human adrenal cortex was presented.

While the mouse X-zone has been shown not to be normally androgenic, its exact function is unknown. Histochemical tests for ketosteroid production have been negative. A summary of some of the known hormonal relationships of the mouse X-zone is as follows: 1) it is independent of the known ovarian hormones estrogen and progesterone; 2) exogenous androgens cause rapid degeneration of the zone; 3) hypophysectomy causes atrophy of the zone but not its immediate and complete disappearance; 4) preparations high in LH activity act directly on the zone (independently of the gonads) to maintain it after hypophysectomy;

* Henry Strong Denison Scholar in Physiology 1953–1954.

5) chorionic gonadotropins act on the X-zone via the ovaries but independently of the hypophysis to cause rapid degeneration of the zone, but estrogen and/or progesterone are probably not the mediating agents; 6) ACTH is not trophic to the zone.

The present study was undertaken with the following aims: 1) to attempt to elucidate further the relationship of pituitary to X-zone, because of the impression that LH action does not explain all the known phenomena, and 2) to determine the relationship, if any, between the X-zone and the permanent cortex. Female litter mates of age 28 days were given daily injections of 1.3 mgm. cortisone intraperitoneally for nine days; female controls from the same litters were given an equal volume of the suspending vehicle on the same schedule. A check on the physiologic activity of the cortisone was secured by noting a depression of body weight gain and a lower adrenal/body weight ratio in the cortisone treated animals. Histological examination revealed atrophy of the fasicular zone of the permanent cortex in the treated animals, as expected; the X-zone, however, was unaffected by the cortisone. On the basis of organ weights it was noted that the uteri of treated animals were significantly smaller than those of the controls, suggesting a depression of growth and/or size maintenance of the uterus by cortisone over long periods of treatment, probably not due to ovarian change alone (short time antagonism has been demonstrated). Further investigation of this finding is being undertaken.

The conclusion drawn from this study was that cortisone has no effect, either directly or via another hormonal axis on the X-zone of the immature female mouse. This offers further confirmation of the independence of X-zone and ACTH. On the basis of this study and what is known of adrenal cortical-pituitary interrelationships, it is suggested that the X-zone is independent in its functioning from the activities of the permanent cortex, a fact not clearly demonstrated by the independence of X-zone and ACTH previously shown.

BIOELECTRIC PHENOMENA AS AN ETIOLOGICAL FACTOR IN INTRAVASCULAR THROMBOSIS

CLARENCE S. WELDON

It has been demonstrated by previous investigators that blood platelets are negatively charged, showing a migration toward the anode in an electric field and that the magnitude of charge is dependant on the relative concentrations of blood proteins. It has been further demonstrated that electrical potential differences are recordable across normal blood vessel walls, and that a reversal of the direction of this potential difference occurs following injury to the vascular wall. These findings suggested that intravascular thrombosis might be due to the electrotactic migration of charged blood platelets in an electric field created by abnormal injury potentials across damaged vascular walls.

Experiments were performed on dog aortae to determine whether thrombi produced by the superimposition of electric current across vessel walls in the direction opposite to that in which it is assumed normally to flow (on the basis of potential differences recorded between intima and adventitia) are quantitatively related to the amount of current passed or the time of passage.

Seventeen aortic experiments are reported: two controls were done with electrodes in place but no current passed; three "semicontrols" were done with current passed in the direction in which it is assumed normally to flow, and twelve with currents from .3 MA to 1.0 MA passed for from 15 min. to 120 min. in the opposite direction (internal electrode positively polarized). The results of these experiments showed that no thrombi formed in the control experiments, that tiny mural thrombi formed in two of the three "semicontrol" experiments and that thrombi were present in 9 of the 12 experimental vessels. A definite

tendency for the size of formed thrombi to increase with increase in the amount of current passed was noted. On histological examination, however, all vessels showing thrombus formation showed varying degrees of necrosis of the vascular wall. It appears that the production of thrombi by this method is due at least in part to the simultaneous production of tissue necrosis, and cannot be offered as evidence for the support of a theory of bioelectric etiology of intravascular thrombosis.

Further studies on measurements of electric activity of normal and damaged aortic walls were done. Potential differences were recorded between the aortic lumen and adventital surface by means of calomel half cell recording electrodes contained in an especially designed apparatus which provided stability, insulation, and isolation of the electrical system. The results of these experiments showed that a potential difference is always recordable in normal vessels, with the lumenal electrode recording negatively to the adventital electrode. However within 3 hours after the vessel is damaged by cutting or crushing a reversal of potential occurs so that the lumenal electrode begins to record positively.

The results of these investigations support the finding that abnormal electrical potential changes occur in damaged blood vessels, but provide no support for the suggestion that thrombus formation following current passage across blood vessel walls is evidence favoring the theory that bioelectric phenomena are etiologic factors in the production of intravascular thrombosis.

EFFECTS OF PROTEOLYTIC ENZYMES AND OF HEPARIN ON BLOOD COAGULATION AND ON ARTERIAL THROMBI

PAUL DIDISHEIM

In view of recent reports by Innerfield et al. on the thrombolytic effects of intravenous trypsin in dogs and on its clinical benefits in various thromboembolic conditions in man, it was of interest to study the effects of proteolytic enzymes on thrombi and on blood coagulation.

In vitro, trypsin and chymotrypsin each digested human and rabbit plasma clots, 1 mg./cc. rendering a clot liquid in 15 to 30 minutes at 37°C. In lower concentrations each markedly shortened clotting time, from 20 minutes to 1½ minutes with .02 mg. trypsin/cc., and to 3 minutes with an equal concentration of chymotrypsin. Higher concentrations prolonged the clotting time to the point of incoagulability. The basis for these two opposite effects, well established for trypsin and probably the same for chymotrypsin, is that in low concentrations these enzymes digest prothrombin to thrombin, which initiates the conversion of fibrinogen to fibrin. In higher concentrations these enzymes further digest and destroy prothrombin, thrombin, and fibrinogen, resulting in prolongation of the clotting time.

The effect of intravenous administration of trypsin and of chymotrypsin on induced arterial thrombi, on prothrombin time and on clotting time was studied in rabbits. Thrombosis was produced by exposing the femoral arteries and injecting thrombin into a 2 cm. ligatured segment. Ligatures were released after 15 minutes and in over 90 per cent of the arteries pulsations stopped and the segment became firm and dark purple.

In a control group of 12 animals with 22 thromboses, half received no treatment and half received intravenous saline daily. All were autopsied and only 1 of 22 thromboses (less than 5 per cent) were found to have recanalized after 1 to 22 (average 9) days. Ten rabbits were administered intravenous trypsin after the production of thromboses. In four, infusion was begun within 35 minutes after thrombosis. Total dosage range was 7.5 to 75 mg. Infusions lasted from 1 to 52 hours. Recanalization occurred in none of the thromboses. The injection of 30 mg. or more of trypsin within 2 hours was invariably fatal, autopsy revealing multiple

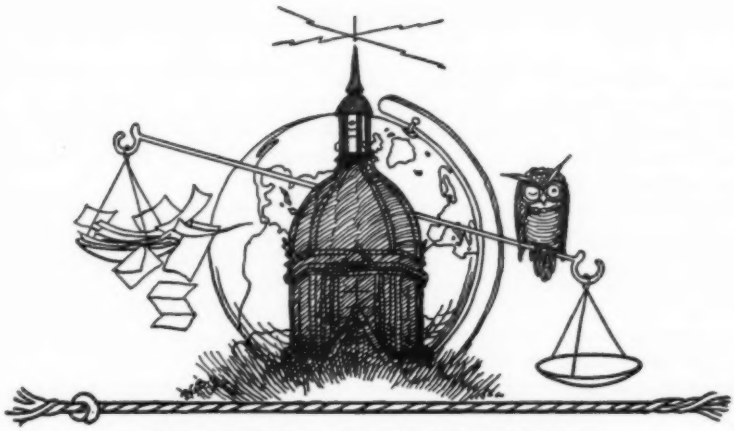
intracardiac and intravascular thromboses, scattered hemorrhages, and in some instances hemothorax and hemoperitoneum. Clotting and prothrombin times were usually, but not always greatly lengthened. Fibrinolysis of clotted blood frequently occurred. In two animals the injection of trypsin directly into the thrombus on three consecutive days had no thrombolytic effect.

Thirty-nine rabbits were administered chymotrypsin, in a similar dosage range, after the production of thromboses. Eight received infusions for 3 to 9 consecutive days. Recanalization occurred in 13 per cent of thrombosed arteries. Twenty-eight per cent of 22 thromboses recanalized when chymotrypsin was begun within 2 hours after thrombosis. The lethal dose and findings on autopsy were similar to those following trypsin, except that hemorrhages were more common and multiple thromboses less common. Probably because of the latter, the rapid injection of large doses was better tolerated than in the case of trypsin. Effects on clotting and prothrombin times, and fibrinolysis, were similar to those following trypsin.

Studies were carried out to determine if lima bean trypsin inhibitor or heparin could block the thrombotic effect of trypsin and chymotrypsin without affecting the thrombolytic effect. Lima bean inhibitor did not do this, but merely increased the amount of enzyme needed to produce these effects in vitro. However heparin, in appropriate concentration diminished the clot accelerating effect of these enzymes, without inhibiting the fibrinolytic effect of higher concentrations. The administration of heparin to animals protected against up to two lethal doses of trypsin.

In 11 rabbits receiving depo-heparin alone following thrombosis, 9 of 20 thrombi, or 45 per cent, recanalized. All recanalizations but one occurred in rabbits that received heparin within 4 hours after thrombosis. After this time heparinization had no effect.

Since trypsin and chymotrypsin in the doses used had slight or no effect on induced arterial thrombi in animals, and since these enzymes produced multiple thromboses and hemorrhages, and profound effects on the clotting mechanism, it is recommended that utmost caution by employed in their clinical use and in the interpretation of reports of their usefulness.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of members of the Editorial Board of this Bulletin)

An Introduction to Human Biochemical Genetics. By H. HARRIS. 96 pp., $2.75. Cambridge University Press, New York.

If the investigations into the nature of the human constitution are to have precision, it is necessary that the effects of genes be measured as directly as possible. Much of genetics of all types has concerned itself with the segregation of genes which control morphological characteristics, and in most cases the exact mode of action of the gene has not been elucidated. In recent years, however, microbiologists and biochemists have directed their attention to the study of gene effects and we now think of genes as controlling unit biochemical processes.

In human genetics, because human populations differ in so many ways from experimental ones, investigative methods have been, of necessity, indirect, but chemical and serologic methods are now proving useful in showing what genes may do in humans.

In this book Dr. Harris has given an up to date review of work and thought in the biochemical aspects of human genetics. It is not a complete review of all contributions and is not intended to be, but rather, it is an analysis of the field citing examples where they illustrate the points being considered. One of the best features of the book are chapters devoted to the principles of genetics which are pertinent to human families and populations. Chapter II deals in simple and lucid form with modes of inheritance and methods of analysis, Chapter III with the heterogeneity of what may appear to be simple characters, and Chapter IX with the variability of manifestation of hereditary characters. This kind of discussion is needed, since the text-books of general genetics are based more upon evidence derived from other species.

The form and arrangement of the book are pleasing and the charts, diagrams and illustrations are good. The book is not long and is very readable.

It seems reasonable to believe that the inherited component of human variation will be subjected to more thorough investigations as methods improve. This book provides a firm foundation on which to base thinking along this line.

BARTON CHILDS

Peripheral Nerve Injuries. Principles and Diagnosis, 2nd edition. By WEBB HAYMAKER AND BARNES WOODHALL. 333 pp., $7.00. W. B. Saunders Co., Philadelphia, Pa.

The first edition of this book, originally drawn up to meet the needs of army medical officers in recognition of peripheral nerve injuries during the last war, provided an excellent guide to diagnosis.

The present volume has been expanded to include recent work on the degree of peripheral nerve injury and its clinical correlation based mainly on Sunderland's studies. There is more material on pain, trophic disorders, contractures and other secondary manifestations of peripheral nerve injuries. Special tests employed in diagnosis have been covered in more detail than in the first edition. There is adequate coverage of the principles of innervation, clinico-pathological classification of peripheral nerve injuries and the clinical features of individual plexus and nerve injuries.

This book is recommended to any one dealing with peripheral nerve trauma.

JOHN W. CHAMBERS

Viruserkrankungen des Menschen. By W. D. GERMER. 190 pp., Ganzleinen DM 30. Georg Thieme Verlag, Stuttgart, Germany.

This book is another welcome addition to the determination of the German medical profession to fill in the gap of information which they were denied during the isolation of the war years. Although it contains only 190 pages, the author has covered the subject well, including all the latest and most pertinent facts from the international literature and at the same time giving mention to less well established observations according to their importance.

The various virus diseases are presented according to the organ systems involved; such as those with exanthemata, those of the central nervous system, skin, eyes, musculature, etc. There is no information included which is not available in English text-books. However, this book has materially condensed the pertinent information concerning virus diseases and is definitely a helpful addition to medical literature. It can certainly be recommended to the German speaking profession as an excellent monograph on virus diseases of man. For others, it will be helpful to note that the German text is written in a clear scientific fashion and is easy to translate into English.

FRANCIS F. SCHWENTKER

The Physician in Atomic Defense. Atomic Principles, Biologic Reaction and Organization for Medical Defense. By THAD P. SEARS. With a Foreword by JAMES J. WARING. 308 pp., $6.00. Year Book Publishers, Chicago, Illinois.

The "atom" whose birth induced the termination of World War II, has also impinged on the physician and, if he is not already confused by atomic pros and cons, Section I of this book should drive him to seek refuge (i.e. Atomic Defense).

The book contains an enviable collection of data on nuclear physics, its many applications, and biological phenomena produced by nuclear radiation and atomic bombs. The author has however couched his description of physical and chemical phenomena in that language of popular writers which is as confusing to the scientist as it is unintelligible to the layman. This is compounded by a liberal use of clinical slang. To a person versed in the mysteries of the square root sign, Einstein's actual equation might mean more than the author's reference to "the mathematical complication expressed in Einstein's theory."

While the data gathered for the book are excellent and extensive, the discussion sheds as little light on their significance as the title does on the subject of the book.

THEODORE ENNS

BOOKS RECEIVED FOR REVIEW

Acute Anuria. A Study Based on Renal Function Tests and Aspiration Biopsy of the Kidney. By CLAUS BRUN. 215 pp., Dan. kr. 30.00. Ejnar Munksgaard, Ltd. Copenhagen, Denmark.

Anatomy for Surgeons, Vol. 1. The Head and Neck. By W. HENRY HOLLINSHEAD. 560 pp., $10.00. Paul B. Hoeber, Inc., New York.

The Billroth I Gastric Resection. With Particular Reference to the Surgery of Peptic Ulcer. By HORACE G. MOORE, JR., AND HENRY N. HARKINS. With a Foreword by DR. COSTA BOHMANSSON and a Preface by DR. JOHN M. WAUGH. 175 pp., $7.50. Little, Brown & Co., Boston, Massachusetts.

Current Therapy 1954. Edited by HOWARD F. CONN. 898 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

Das Bild des Menschen in der Psychiatrie. By KURT KOLLE. 37 pp., kartoniert DM 2.50 (.60). Georg Thieme Verlag, Stuttgart, Germany.

Die Halswirbelsäule. Pathologie und Klinik. By GERHARD EXNER. 140 pp., Ganzleinen DM 21.60 ($5.15). Georg Thieme Verlag, Stuttgart, Germany.

An Introduction to Pathology and Bacteriology—For Medical Students in the Tropics. By the late E. C. SMITH. Revised by R. KIRK, 2nd edition. 390 pp., $9.00. Staples Press, New York.

The Jealous Child. By EDWARD PODOLSKY. 147 pp., $3.75. Philosophical Library, New York.

Manual of Clinical Mycology. By NORMAN F. CONANT, DAVID TILLERSON SMITH, ROGER DENIO BAKER, JASPER LAMAR CALLAWAY AND DONALD STOVER MARTIN. 456 pp., $6.50. W. B. Saunders Co., Philadelphia, Pa.

Mayo Clinic Diet Manual, 2nd edition. By Committee on Dietetics of the Mayo Clinic. 247 pp., $5.50. W. B. Saunders Co., Philadelphia, Pa.

Nurse and Patient. By EVELYN C. PEARCE. 182 pp., $3.00. J. B. Lippincott Co., Philadelphia, Pa.

Phasenkontrast-Hämatologie. By HANS FRANKE. 75 pp., kartoniert DM 9.60 ($2.30). Georg Thieme Verlag, Stuttgart, Germany.

The Process of Psychotherapy. By HARRINGTON V. INGHAM AND LEONORE R. LOVE. 270 pp., $5.00. McGraw-Hill Book Co., New York.

Problems of Consciousness. Transactions of the Fourth Conference, March 29, 30 and 31, 1953. Edited by HAROLD A. ABRAMSON. 177 pp., $3.25. The Josiah Macy, Jr. Foundation, New York.

The Psychiatric Aide. His Part in Patient Care. By ALICE ROBINSON. 186 pp., $3.00. J. B. Lippincott Co., Philadelphia, Pa.

Reconstructive Surgery of the Eyelids, 2nd edition. By WENDELL L. HUGHES. 260 pp., $8.50. The C. V. Mosby Co., St. Louis, Missouri.

Surgical Infections. Prophylaxis Treatment. Antibiotic Therapy (American Lecture Series). By EDWIN J. PULASKI. 315 pp., $7.75. Charles C Thomas, Springfield, Illinois.

INDEX TO VOLUME XCIV

Pagination according to months:
January, 1954, 1–50
February, 1954, 51–116
March, 1954, 117–167
April, 1954, 169–225
May, 1954, 227–287
June, 1954, 289–360

Abscesses and Cavities of the Lung. A Clinical Consideration of (Thayer Lecture I for 1953).. 227
Abstracts of Papers Presented Before The Johns Hopkins Medical Society.
Dec. 14, 1953 and Jan. 11, 1954 158
Feb. 8, and Mar. 8, 1954 218
April 12, 1954 348
Activity of Single Neurons in the Tactile Thalamic Region of the Cat in Response to a Transient Peripheral Stimulus. Rose, Jerzy E. and Mountcastle, Vernon B. 238
Amberson, J. Burns: A Clinical Consideration of Abscesses and Cavities of the Lung (Thayer Lecture I for 1953) 227
The Evolution of Pulmonary Tuberculosis and Its Behavior Under Treatment (Thayer Lecture II for 1953) 337
Amino Compounds, Primary. The Multiplicity of Plasmin Inhibitors in Human Serum Demonstrated by the Effect of 169
Anastomosis, End to End, Between the Left Subclavian and Left Pulmonary Artery. Simultaneous Dye Dilution and Fick Determinations of Left and Right Ventricular Outputs in Dogs with 199
Aperiodic Ballistocardiograph. Talbot, S. A., Deuchar, D. C., Davis, F. W. Jr., and Scarborough, W. R. 27
Appleby, R. E.: (see Otto, G. F.) 319
Asper, Samuel P. Jr.: (see Wiswell, John G.) 94

Barnes, F. W. Jr.: (see Nisonoff, A.) 117
Berthrong, Morgan: (see Howard, John Eager) 51
(see Otto, G. F.) 319
Billings, F. T. Jr.: The Induction of Sarcoid-Like Lesions by the Injection of Tuberculin 139
Bongiovanni, Alfred M.: A Simplified Method for the Routine Determination of Pregnanediol and Pregnanetriol in Urine 180
Book Reviews 45, 110, 162, 222, 283, 353

Capillaria Hepatica Infection. Eosinophilia and Hepatomegaly Due to 319
Clayton, George W. Jr.: (see Bongiovanni, Alfred M.) 180
Clinical Consideration of Abscesses and Cavities of the Lung (Thayer Lecture I for 1953). Amberson, J. Burns 227
Clinical Features of the Genetic Variants of Sickle Cell Disease. Smith, Ernest W., and Conley, C. Lockard 289
Collins, Harold A.: (see Pearce, Morton Lee) 199
Conley, C. Lockard: (see Smith, Ernest W.) 289
Corddry, Ellen G.: (see Grafflin, Allan L.) 1, 22
Vascular Patterns in the Human Retina 148

Davis, F. W. Jr.: (see Talbot, S. A.) 27
Deuchar, D. C.: (see Talbot, S. A.) 27
Diabetes. Hospital Data on the Birth of Large Infants to "Prediabetic Women" 128

Effects of L-Triiodothyronine and L-Thyroxine on the Metabolism of Tissues in Vitro. Wiswell, John G., Zierler, Kenneth L., Fasano, Mary B. and Asper, Samuel P. Jr. 94
Embolization, Massive Pulmonary, by Cerebral Cortical Tissue 86
Enns, T.: (see Nisonoff, A.) 117
Enzymatic Transamination. Mechanisms in. Reaction Between Carbon Chains of Same Length .. 117
Eosinophilia and Hepatomegaly Due to Capillaria Hepatica Infection. Otto, G. F., Berthrong, M., Appleby, R. E., Rawlins, J. C. and Wilbur, Oscar 319
Evolution of Pulmonary Tuberculosis and Its Behavior Under Treatment (Thayer Lecture II for 1953). Amberson, J. Burns 337

Fasano, Mary B.: (see Wiswell, John G.) 94
Fick Determinations and Simultaneous Dye Dilutions of Left and Right Ventricular Outputs in Dogs with End to End Anastomosis Between the Left Subclavian and Left Pulmonary Artery 199
Futcher, P. H.: Hospital Data on the Birth of Large Infants to "Prediabetic" Women 128

Gardner, Lytt I.: Role of Human Plasma Protein Fractions IV and V in 17-Ketosteroid Transport. Preliminary Report 105
Genetic Variants of Sickle Cell Disease. Clinical Features of the 289
Goldman, Leon: (see Turner, Thomas B.) 204
Gordon, Harry H.: Observations on the Etiology of Retrolental Fibroplasia 34
Gould, David M.: (see Howard, John Eager) 51
Grafflin, Allan L.: In Vivo Studies of the Frog's Liver During the Excretion of Thioflavine S and Vasoflavine 1
In Vivo Studies of the Frog's Liver During the Excretion of Esculin 22

Hepatomegaly and Eosinophilia Due to Capillaria Hepatica Infection 319
Hix, Ivan: (see Gordon, Harry H.) 34
Hospital Data on the Birth of Large Infants to "Prediabetic" Women. Futcher, P. H. and Long, N. W. Jr. 128
Howard, John Eager: Hypertension Resulting from Unilateral Renal Vascular Disease and Its Relief by Nephrectomy 51
Hypertension Resulting from Unilateral Renal Vascular Disease and Its Relief by Nephrectomy. Howard, John Eager, Berthrong, Morgan, Gould, David M. and Yendt, Edmund R. . 51

Immunization Against Tetanus. Studies on the Duration of Protection Afforded by 204
In Vivo Studies of the Frog's Liver During the Excretion of Thioflavine S and Vasoflavine. Grafflin, Allan L. and Corddry, Ellen G. 1
In Vivo Studies of the Frog's Liver During the Excretion of Esculin. Grafflin, Allan L. and Corddry, Ellen G. 22
Induction of Sarcoid-Like Lesions by the Injection of Tuberculin. Billings, F. T. Jr. and Shapiro, John L. 139

Lepow, I. H.: (see Ratnoff, Oscar D.) 169
Long, N. W. Jr.: (see Futcher, P. H.) 128
Lubchenco, Lula: (see Gordon, Harry H.) 34
Liver, Frog's. In Vivo Studies of During the Excretion of Thioflavine S and Vasoflavine 1
In Vivo Studies of During the Excretion of Esculin 22

Massive Pulmonary Embolization by Cerebral Cortical Tissue. Oppenheimer, Ella H. 86
McKusick, Victor A.: Spectral Phonocardiography: Problems and Prospects in the Application of the Bell Sound Spectrograph to Phonocardiography 187
Mechanisms in Enzymatic Transamination. Reaction Between Carbon Chains of Same Length. Nisonoff, A., Barnes, F. W. Jr., Enns, T. and von Schuching, S. 117

Metabolism of Tissues in Vitro. The Effects of L-Triiodothyronine and L-Thyroxine on..... 94
Mountcastle, Vernon B.: (see Rose, Jerzy E.)..... 238
Multiplicity of Plasmin Inhibitors in Human Serum, Demonstrated by the Effect of Primary Amino Compounds. Ratnoff, Oscar D., Lepow, I. H. and Pillemer, Louis..... 169

Nephrectomy. Hypertension Resulting from Unilateral Renal Vascular Disease and Its Relief by..... 51
Neurons, Single, in the Tactile Thalamic Region of the Cat in Response to a Transient Peripheral Stimulus. Activity of..... 238
Newman, Elliot V.: (see Pearce, Morton Lee)..... 199
Nisonoff, A.: Mechanisms in Enzymatic Transamination. Reaction Between Carbon Chains of Same Length..... 117

Observations on the Etiology of Retrolental Fibroplasia. Gordon, Harry H., Lubchenco, Lula and Hix, Ivan..... 34
Oppenheimer, Ella H.: Massive Pulmonary Embolization by Cerebral Cortical Tissue..... 86
Otto, G. F.: Eosinophilia and Hepatomegaly Due to Capillaria Hepatica Infection..... 319

Pearce, Morton Lee: Simultaneous Dye Dilution and Fick Determinations of Left and Right Ventricular Outputs in Dogs with End to End Anastomosis Between the Left Subclavian and Left Pulmonary Artery..... 199
Peripheral Stimulus, Transient. Activity of Single Neurons in the Tactile Thalamic Region of the Cat in Response to a..... 238
Phonocardiography. Problems and Prospects in the Application of the Bell Sound Spectrograph to..... 187
Pillemer, Louis: (see Ratnoff, Oscar D.)..... 169
Plasma Protein Fractions IV and V in 17-Ketosteroid Transport, Role of. Preliminary Report..... 105
Plasmin Inhibitors in Human Serum Demonstrated by the Effect of Primary Amino Compounds. The Multiplicity of..... 169
Pregnanediol and Pregnanetriol in Urine. A Simplified Method for the Routine Determination of..... 180
Proceedings of the Meeting of the Johns Hopkins Medical Society, Monday, November 9, 1953..... 108

Ratnoff, Oscar D.: The Multiplicity of Plasmin Inhibitors in Human Serum, Demonstrated by the Effect of Primary Amino Compounds..... 169
Rawlins, J. C.: (see Otto, G. F.)..... 319
Renal Vascular Disease, Unilateral. Hypertension Resulting from and Its Relief by Nephrectomy..... 51
Retina. Vascular Patterns in the Human..... 148
Retrolental Fibroplasia. Observations on the Etiology of..... 34
Role of Human Plasma Protein Fractions IV and V in 17-Ketosteroid Transport. Preliminary Report. Gardner, Lytt I..... 105
Rose, Jerzy E.: Activity of Single Neurons in the Tactile Thalamic Region of the Cat in Response to a Transient Peripheral Stimulus..... 238

Sarcoid. The Induction of Sarcoid-Like Lesions by the Injection of Tuberculin..... 139
Scarborough, W. R.: (see Talbot, S. A.)..... 27
Scott, H. William, Jr.: (see Pearce, Morton Lee)..... 199
Shapiro, John L.: (see Billings, F. T. Jr.)..... 139
Sickle Cell Disease. Clinical Features of the Genetic Variants of..... 289
Simplified Method for the Routine Determination of Pregnanediol and Pregnanetriol in Urine. Bongiovanni, Alfred M. and Clayton, George W. Jr..... 180

Simultaneous Dye Dilution and Fick Determinations of Left and Right Ventricular Outputs in Dogs with End to End Anastomosis Between the Left Subclavian and Left Pulmonary Artery. Pearce, Morton Lee, Collins, Harold A., Scott, H. William, Jr. and Newman, Elliot V. 199
Smith, Ernest W.: Clinical Features of the Genetic Variants of Sickle Cell Disease 289
Spectral Phonocardiography: Problems and Prospects in the Application of the Bell Sound Spectrograph to Phonocardiography. McKusick, Victor A., Talbot, Samuel A. and Webb, George N. 187
Stafford, Edward S.: (see Turner, Thomas B.) 204
Studies on the Duration of Protection Afforded by Active Immunization Against Tetanus. Turner, Thomas B., Stafford, Edward S. and Goldman, Leon 204

Talbot, S. A.: The Aperiodic Ballistocardiograph 27
Talbot, Samuel A.: (see McKusick, Victor A.) 187
Tetanus. Studies on the Duration of Protection Afforded by Active Immunization Against 204
Thayer Lectures for 1953.
I. A Clinical Consideration of Abscesses and Cavities of the Lung. Amberson, J. Burns 227
II. The Evolution of Pulmonary Tuberculosis and Its Behavior Under Treatment 337
Triiodothyronine and Thyroxine on the Metabolism of Tissues in Vitro. The Effects of 94
Tuberculosis and Its Behavior Under Treatment. The Evolution of (Thayer Lecture II for 1953) 337
Turner, Thomas B.: Studies on the Duration of Protection Afforded by Active Immunization Against Tetanus 204

Vascular Patterns in the Human Retina. Corddry, Ellen G. 148
von Schuching, S.: (see Nisonoff, A.) 117

Webb, George N.: (see McKusick, Victor A.) 187
Wilbur, Oscar: (see Otto, G. F.) 319
Wiswell, John G.: The Effects of L-Triiodothyronine and L-Thyroxine on the Metabolism of Tissues in Vitro 94

Yendt, Edmund R.: (see Howard, John Eager) 51

Zierler, Kenneth L.: (see Wiswell, John G.) 94

restlessness and irritability with pain

one of the 44 uses

for short-acting **Nembutal**

"OF the various drugs used, codein and NEMBUTAL (*Pentobarbital, Abbott*) were found to be highly effective. It was found that these drugs could be repeated to provide continued restfulness and that fractions of the original doses were often effective as maintenance doses.

"They usually produce rest and the sleep brought about by their use approximates normal sleep. The action of these drugs is rapid; and if the patient is not disturbed, the sleep may continue from one to five hours."[1]

Abbott

1. Gurdjian, E. S., and Webster, J. E., Amer. J. of Surgery, 63:236, 1944.

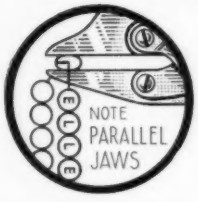
406118A

(In writing advertisers, please mention the Bulletin.)

Surgical and Hospital Specialties BY BERBECKER

SIDE-CUTTING PLIER
—for cutting Surgical Wires & Pins

Cutters are on the outside. Wire to be cut may be reached with entire freedom from interference. When opening and closing, the jaws remain parallel. Round objects may be gripped without chance of slipping. Made in England of high grade, tempered steel, and heavily nickeled to withstand rust. Overall length, 5". Ask your dealer for No. 505.



IDEAL BABY BEAD "CRUSHER"

High leverage enables nurse to easily seal the split bead in baby identification bracelets. Parallel jaws prevent the bead from slipping.

BERBECKER SURGEONS' NEEDLES

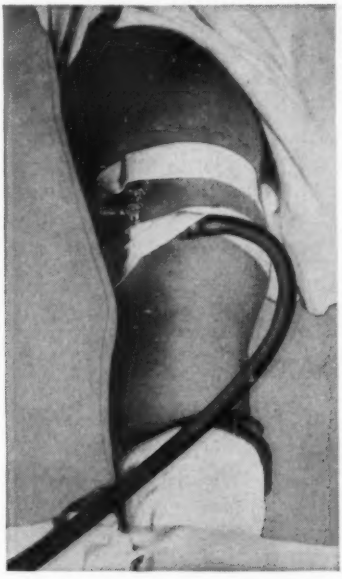
Made in England for the Surgeons and Hospitals of America

JULIUS BERBECKER & SONS, INC., 15 E. 26th ST., NEW YORK 10

An everyday custom that gave new meaning to a minute

Once an idle minute was only a minute . . . until Coca-Cola put it to work for you. A pause for ice-cold Coca-Cola became the pause that refreshes—that little minute long enough for a big rest.

Coca-Cola, an honestly made product of an intrinsic quality, is a drink that performs a pleasant everyday service to millions in every walk of life.



WYDASE SPEEDS FLUID ABSORPTION

• *In Hypodermoclysis* • *In Local Edema*

Hypodermoclysis: WYDASE permits subcutaneous infusion at approximately the intravenous rate. For WYDASE is an enzyme that vastly increases tissue permeability and speeds the circulatory transfer of injected fluids. WYDASE makes hypodermoclysis widely practical, of special value in numerous contraindications to intravenous therapy. Spares the veins, minimizes tissue distention and pain, permits prolonged infusion.

Local Edema: WYDASE speeds resorption of accumulated transudates and blood. Indications include traumatic edema, hematoma, paraphimosis, myxedematous pretibial swelling.

Wyeth®
Philadelphia 2, Pa.

LYOPHILIZED
WYDASE®
HYALURONIDASE

SUPPLIED:
Vials of 150 and 1500 TR (turbidity-reducing) units
ALSO AVAILABLE:
Solution WYDASE.
Vials of 1 cc., 150 TR units

THE

HENRY B. GILPIN

COMPANY

FULL LINE SERVICE ✶ WHOLESALE DRUG HOUSE.

✶ DISTRIBUTORS OF LABORATORY CHEMICALS. ✶

ESTABLISHED 1845.

Now in its third, completely revised edition!

MANUAL OF APPLIED NUTRITION

Dietary Department of the Johns Hopkins Hospital

"A useful addition . . . The information in the book is concise, practical, well organized and of a convenient size."

Journal of the American Dietetic Association

"This valuable diet formulary . . . is practical, scientific, and realistic as well as succinct and concise and can easily serve as a model for any modern hospital."

New York State Journal of Medicine

96 pages **Alphabetized Table of Contents** **Appendix** **Paper, $2.50**

Order from:

THE JOHNS HOPKINS PRESS **Baltimore 18, Maryland**

(In writing advertisers, please mention the Bulletin.)

Meets the Acid Test!

Unexcelled for the treatment and management of

PEPTIC ULCER and GASTRIC HYPERACIDITY

Assures:

- Freedom from constipation.
- Prompt and sustained relief.
- Greater neutralizing capacity.
- Adequate phosphate to prevent depletion.

Literature and Samples Available on Request.

Supplied in 16 fl. oz. bottles and bottles of 64 tablets.

WINTON
WINTON
ALUGEL
BRAND OF
ALUMINUM HYDROXIDE GEL
AND
MAGNESIUM PHOSPHATE TRIBASIC 4%
ALUGEL is a palatable combination of colloidal Aluminum Hydroxide with tribasic Magnesium Phosphate. .
The Aluminum Hydroxide in this product acts as an effective antacid and absorbent in the neutralization of excess stomach acid.
The Magnesium Phosphate acts as an effective antacid and supplies essential phosphate element.
Indicated in treatment of gastric hyperacidity
AVERAGE DOSE—One or two teaspoonfuls to be taken 5 or 6 times daily between meals and upon retiring or as directed by physician.
SHAKE BOTTLE WELL KEEP FROM FREEZING
RALPH WINTON CO.
BALTIMORE, MARYLAND

RALPH WINTON CO. *Pharmaceutical Chemists* · **BALTIMORE 2, MD.**

(In writing advertisers, please mention the Bulletin.)

the secret of sleep in a capsule

PULVULES

'Seconal Sodium'

(Secobarbital Sodium, Lilly)

rapid action . . .
short duration . . .
awaken refreshed

SUPPLIED IN PULVULES

No. 318	**1/2 gr. (0.0325 Gm.)**
No. 243	**3/4 gr. (0.05 Gm.)**
No. 240	**1 1/2 grs. (0.1 Gm.)**

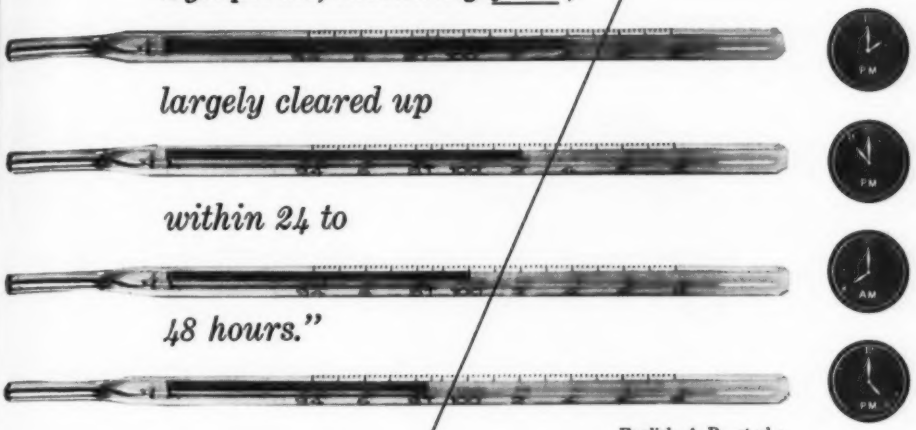
DOSAGE:

Insomnia, 1 1/2 grs. Preoperative hypnotic, 3 to 4 1/2 grs. O. B., 3 to 4 1/2 grs. initially, followed by 1 1/2 to 3 grs. at one to three-hour intervals. Not more than 12 grs. in twenty-four hours.

ELI LILLY AND COMPANY, INDIANAPOLIS 6, INDIANA, U. S. A.

(In writing advertisers, please mention the Bulletin.)

"*Symptoms, including fever,*



largely cleared up within 24 to 48 hours."

English, A. R., et al.: Antibiotics Annual (1953-1954), New York, Medical Encyclopedia, Inc., 1953, p. 70.

AIH *afebrile in hours* — **Tetracyn** hydrochloride

Brand of tetracycline hydrochloride

a new broad-spectrum antibiotic of unexcelled tolerance

Simple, dramatic proof of the effectiveness of Tetracyn is offered by the characteristic rapid defervescence noted in the treatment of a wide range of susceptible infectious diseases. *Think of Tetracyn* whenever you take a temperature for an AIH response in Tetracyn-sensitive infections.

TETRACYN TABLETS
(*sugar coated*) 250 mg., 100 mg., 50 mg.

ROERIG Rx

BASIC PHARMACEUTICALS FOR NEEDS BASIC TO MEDICINE

536 Lake Shore Drive, Chicago 11, Illinois

Daytime sedation
with
mental alertness

WINTHROP

MEBARAL®
BRAND OF MEPHOBARBITAL

—in depressed and agitated states

psychoneurosis
hypertension
hyperthyroidism
convulsive disorders
difficult menopause
hyperhidrosis

Neurotic depression hiding beneath the disguise of multiple physical complaints is an everyday problem in medical practice.

For effective sedation in these cases, and as a means of restoring harmonious relations between patient and environment, Mebaral has been found especially suitable because it lacks excessive hypnotic action.

DOSAGE:
Adults—32 mg. to 0.1 Gm. (optimal 50 mg.), 3 or 4 times daily.

Children—16 to 32 mg., 3 or 4 times daily.

SUPPLIED:
Tablets of 32 mg. (½ grain)
50 mg. (¾ grain)
0.1 Gm. (1½ grains)
0.2 Gm. (3 grains) scored

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Mebaral, trademark reg. U. S. & Canada

WINTHROP-STEARNS INC. New York 18, N. Y. · Windsor, Ont.

The McCollum-Pratt Institute

SYMPOSIUM OF JUNE, 1953

MECHANISM OF ENZYME ACTION

Edited by **William D. McElroy and Bentley Glass**

During the past thirty years remarkable progress has been made in the isolation and identification of intermediates, necessary enzymes and coenzymes of a large number of biochemical reactions. The availability of isotopes and large quantities of purified enzymes has made it feasible to study in some detail the mechanisms involved in these processes. In recent years such studies have led to the idea that some enzymes enter as reactants, functioning to preserve bond energy. Contributions to this symposium from the physical chemists, organic chemists, protein chemists, and enzymologists further emphasize the importance of the catalytic protein as a reactant in biochemical transformations. More than a hundred scientists participated in this symposium.

1. **PROTEIN CONFIGURATION AND BIOLOGICAL ACTIVITY**—*papers by* M. Heidelberger, J. G. Kirkwood, R. M. Herriott, H. Neurath, J. A. Gladner, E. W. Davie, and W. Kauzmann.

2. **KINETICS OF ENZYME-CATALYZED REACTIONS**—*papers by* H. Eyring, R. Lumry, J. D. Spikes, H. B. Bull, J. S. Friedenwald, and G. D. Maengwyn-Davies.

3. **THE FUNCTION OF METALS IN ENZYME CATALYSIS**—*papers by* M. Calvin, I. M. Klotz, E. L. Smith, N. C. Davis, E. Adams, and D. H. Spackman.

4. **THE MECHANISM OF ELECTRON AND HYDROGEN TRANSPORT**—*papers by* F. H. Westheimer, B. Vennesland, B. Chance, and R. R. Ferguson.

5. **THE FUNCTION OF ENZYMES IN GROUP TRANSFER**—*papers by* F. Lipmann, E. Racker, S. F. Velick, P. D. Boyer, H. L. Segal, I. C. Gunsalus, E. R. Stadtman, D. E. Koshland, Jr., I. B. Wilson, W. H. Harrison, and H. M. Kalckar.

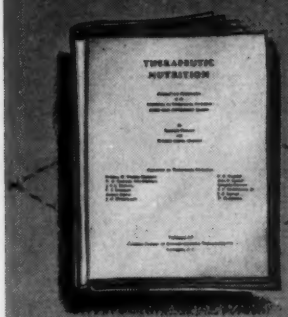
6. **SUMMARY**, by Bentley Glass.

836 pages | Author & Subject Index | February, 1954 | $11.00

Order today from

THE JOHNS HOPKINS PRESS • Baltimore 18, Maryland

NEW NATIONAL RESEARCH COUNCIL STANDARDS* for effective vitamin therapy



Emphasizing that regular vitamin intake is essential to productive health and that stresses such as disease and injury profoundly affect nutritional requirements, the Committee on Therapeutic Nutrition of the Food and Nutrition Board* recommends standard vitamin formulations for both maintenance and therapeutic dosage. In Panalins and Panalins-T, Mead Johnson & Company makes these authoritatively recommended formulations available to the medical profession.

for vitamin therapy in stress situations

PANALINS-T

N.R.C. STANDARD THERAPEUTIC VITAMIN CAPSULE

Each Panalins-T capsule supplies:

Thiamine	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Calcium pantothenate	20 mg.
Pyridoxine	2 mg.
Folic acid	1.5 mg.
Ascorbic acid	300 mg.
Vitamin B_{12}	4 mcg.

1 or 2 capsules daily.
Bottles of 30 and 100.

Panalins-T supplies important water-soluble vitamins in the high therapeutic potencies needed to promote optimal recovery from disease or injury. Since the body cannot store appreciable amounts of these vitamins, regular provision of generous amounts is essential.

to safeguard and maintain vitamin nutrition

PANALINS

N.R.C. STANDARD MAINTENANCE VITAMIN CAPSULE

Each Panalins capsule supplies:

Thiamine	2 mg.
Riboflavin	2 mg.
Niacinamide	20 mg.
Ascorbic acid	50 mg.
Calcium pantothenate	5 mg.
Pyridoxine	0.5 mg.
Folic acid	0.25 mg.
Vitamin B_{12}	2 mcg.
Vitamin A	5000 units
Vitamin D	400 units

1 or 2 capsules daily.
Bottles of 100 and 500.

Panalins supplies protective potencies of ten vitamins needed for maintenance of the good vitamin nutrition essential to productive health.

* Therapeutic Nutrition, Committee on Therapeutic Nutrition, Food and Nutrition Board, Publication 234, National Research Council.

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD